Archives of Internal Medicine

VOLUME 45 FEBRUARY, 1930 NUMBER 2

LYMPHOMA

A STUDY OF ONE HUNDRED AND FIFTY CASES *

C. W. BALDRIDGE, M.D.
AND
C. D. AWE, M.D.
IOWA CITY

The recent medical literature contains many reports dealing with the unusual manifestations [1] of that disease which is characterized by progressive enlargement of the fixed lymphatic tissue and a fatal termination. It has no doubt occurred to most clinicians who are interested in this subject that the unusual manifestations are being reported without any definite idea as to what comprises the usual. For this reason, we feel that the information derived from the study of 150 consecutive cases in the University Hospital might be worth recording. The data obtained in our study will be presented in tabular form, and the discussion of obvious facts will be avoided.

No generally accepted terminology for the conditions under consideration exists. One finds clinical classifications and classifications based on pathologic histology as well as attempts to combine the two. Etiology remains a matter of opinion,[2] and pathologic concepts are often almost lost in a maze of names. We have heard the term "malignant lymphoma" given two different meanings by members of the same hospital staff. Because of the existing confusion, every one discussing the subject must either explain his terminology at length or accept the risk of being misunderstood.

We do not wish to discuss terminology or to defend that which we shall use in this communication. We shall use the terminology with which we are familiar and supplement each term with a few common synonyms when such exist.

Lymphoma (lymphoblastoma) (malignant lymphoma)
1. Sclerosing type (Hodgkin's disease) (lymphogranuloma)
2. Endothelial type (lympho-epithelioma)
3. Lymphoblastic type (lymphosarcoma)
4. Lymphocytic type
   With leukemia (lymphatic leukemia) (lymphocytic leukemia)
   Without leukemia (pseudoleukemia) (aleukemic leukemia)

* Submitted for publication, June 18, 1929.

* From the Department of Internal Medicine, University of Iowa.

1. Barron, M.: Unique Features of Hodgkin's Disease (Lymphogranulomatosis) with Report of Three Unusual Cases and a Summary of Twenty-Four Cases Studied at Necropsy, Arch. Path. **2**:659 (Nov.) 1926. Holmes, G. W.: Unusual Manifestations of Lymphoblastoma, Am. J. Roentgenol. **16**:107, 1926.

2. Simonds, J. P.: Hodgkin's Disease, Arch. Path. **1**:394 (March) 1926.

Table 1 gives the number of cases falling into each group, together with the number of biopsies and necropsies.

Microscopic sections from thirty-nine complete and five partial necropsies and sixty-nine biopsies were restudied for this communication. The division of cases into the four principal types has been based on pathologic changes, except in twenty-five of the cases of lymphatic leukemia. Blood manifestations characteristic of lymphatic leukemia are so uniformly associated with the lymphocytic type of histologic change that we have accepted such manifestations in lieu of histologic study of lymph nodes in these twenty-five cases.

In situ, lymphomatous nodes have certain definite characteristics. They are usually firm, smooth, freely movable and not tender. The nodes vary in consistency, those in the sclerosing and endothelial types being hardest, but even these nodes are not as hard as those in metastatic carcinoma. The smooth surface and uniform density of lymphomatous nodes are in contrast with the irregular masses of scar tissue, fibrosed

TABLE 1.—*Types of Lymphoma*

	Cases	Biopsies	Necropsies	Cases Studied Histologically
Sclerosing type	46	36	15	46
Endothelial type	2	3	1	2
Lymphoblastic type	19	15	5	19
Lymphocytic type with leukemia	55	13	19	30
Lymphocytic type without leukemia	14	11	4	14
Unclassified*	14	0	0	0
Total	150	78	44	111

* Neither biopsy nor necropsy was done and blood manifestations were not those of leukemia.

fat and small lymph nodes often felt in the normal axilla. The expansive growth without periadenitis makes the early nodes of all types of lymphoma freely movable, contrasting again with the anchored nodes of old inflammation. Tuberculous lymph nodes are apt to be linked together in a chain by the thickened lymphatics which connect them. Tuberculous cervical lymph nodes are often freely movable from side to side, but movement up or down causes distinct tension on neighboring nodes. Tenderness, such as is characteristic of the lymph nodes in glandular fever and in other acute infectious conditions, is not seen in lymphoma.

The gross appearance of lymphomatous nodes removed at biopsy is often diagnostic. In addition to the enlargement, the hilum is pressed out, the capsule is tight, and the density is often increased. On section, the appearance varies in the different types. The appearance of the sclerosing type will depend on the amount of fibrosis and necrosis; the endothelial type may suggest carcinoma because of a light gray granular appearance; and the lymphoblastic and lymphocytic types show a uniform cut surface which is obviously cellular.

The sclerosing type with its fibrosis, giant cells and usually eosinophils and necrotic areas is quite easily recognized histologically, though it is possible to find rather marked quantitative variations in its elements (fig. 1). The endothelial type, which is apparently uncommon, contains areas of irregularly shaped cells with vesicular nuclei and abundant, poorly staining cytoplasm. In some of the nodes from one of our cases,

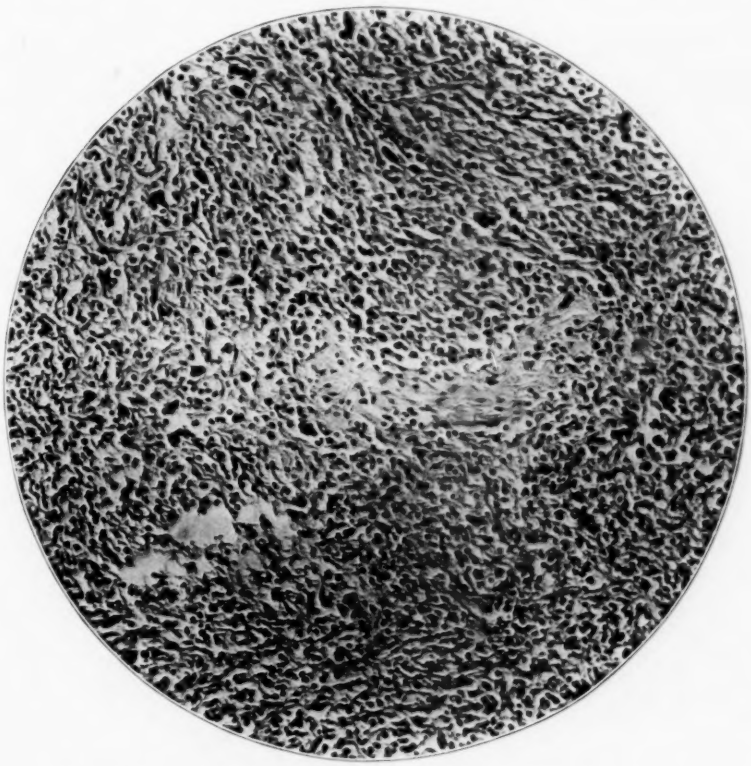

Fig. 1.—Sclerosing type of lymphoma. Numerous giant cells, both mononucleated and multinucleated and diffuse fibrosis are the outstanding features. This section also showed great numbers of eosinophils and a few small areas of necrosis. In long-standing cases, the fibrosis is usually in coarse bands.

the pathologic change was not unlike that seen in metastatic carcinoma (figs. 2 and 3). Ewing [3] and others feel that the syncytial cells are epithelial rather than endothelial. Sections of nodes from the lympho-

3. Ewing, James: Lymphoepithelioma, Am. J. Path. **5**:99, 1929.

cytic type give the appearance of a sac full of cells. The lymphoblastic type is quite similar, except that the cells are less uniform. In both these types the growth, which is expansive, obliterates the hilum and peripheral sinus, thus distorting the architecture beyond recognition.

In our series, invasion of the capsule and surrounding tissue has not been a reliable criterion in diagnosis of the lymphoblastic type (lympho-

Fig. 2.—Endothelial type. The histologic picture seen in most of the enlarged nodes and in the metastatic lesions in the viscera. The cytoplasm of the cells is not well shown in the photograph.

sarcoma). The main difference between the lymphoblastic and lymphocytic types lies in the character of the cells making up the nodes (figs. 4 and 5). As one might expect, the cells are occasionally intermediate in character, and such borderline cases are so difficult of classification as to make this particular division seem artificial. The difficulty is most marked in lymphatic leukemia in childhood, in which the lymphoid cells

comprising the nodes are often larger and have slightly more cytoplasm than the cells seen in the lymphatic leukemia of adults. We have never discovered more than one type of pathologic change in the same patient.

Table 2 represents a study of the age and sex in the various types. The age at onset has been used in all instances. In the whole group of 150 cases, there were 101 males and 49 females, or a ratio of about 2 : 1.

Fig. 3.—Endothelial type, showing an area which has a striking resemblance to carcinoma in the appearance of cells, in their arrangement and in fibrous tissue reaction to their presence. Under higher magnifications, however, these groups of cells have the appearance of a syncytium, and relationship to the fibrous tissues is not the same as that between carcinoma cells and stroma. This section is from one of the nodes first enlarged which was removed about three months after irradiation. Two biopsies and a complete necropsy were done on this patient. No evidence of a primary carcinoma was found. The existence of an uninterrupted series of intermediate steps between the two extremes led to the conclusion that the sections pictured represent different phases of the same tumor.

In a larger series reported by Minot and Isaacs,[4] males predominated 2.12:1. It will be noted that the females were in most types younger than the males. This feature was also mentioned by Minot and Isaacs. Lymphatic leukemia was especially common in old men and, strangely

TABLE 2.—*Age and Sex in Various Types*

	Cases	Average Age	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Sclerosing type	46	29								
Male	28	30	2	5	10	4	4	3	..	..
Female	18	25	1	1	12	3	..	1	..	..
Endothelial type	2	23								
Male	2	23	1	..	..	1	..	..	..	..
Female	..	..	..	..	..	..	..	..	..	..
Lymphoblastic type	19	45								
Male	12	44	..	2	3	..	1	1	5	..
Female	7	46	1	..	..	1	1	2	2	..
Lymphocytic type with leukemia	55	37								
Male	40	42	8	2	1	2	7	7	11	2
Female	15	24	7	2	..	1	2	2	1	..
Lymphocytic type without leukemia	14	40								
Male	11	44	..	..	1	3	3	2	2	..
Female	3	26	..	1	1	1	..	..	..	..
Total	136	..	20	13	28	16	18	18	21	2

TABLE 3.—*Duration of Disease*

	Cases	Number Followed to Death	Average Duration in Years	Longest Duration in Years	Shortest Duration in Years	Sex	Cases	Average Duration in Years
Sclerosing type	46	27	2.15	9	0.16	M	13	2.24
						F	14	2.08
Endothelial type	2	1	3	...	....	M	1	3
						F	..	....
Lymphoblastic type	19	12	1.24	5	0.16	M	8	1.5
						F	4	0.7
Lymphocytic type								
With leukemia								
Adult	35	21	3.17	9	0.25	M	17	3.0
						F	4	3.9
Child	20	16	0.43	0.8	0.08	M	8	0.35
						F	8	0.52
Without leukemia	14	7	2.19	11	0.25	M	5	0.69
						F	2	6.1

enough, there were only two instances of its occurrence in patients between the ages of 11 and 38, both men, one 19 and the other 21.

The duration of the illness (table 3), was estimated from the date of the discovery of enlarged nodes or the onset of definite symptoms. It will be observed that the progression of lymphatic leukemia was relatively slow in the adult, whereas in the child it was rapidly fatal. In general,

4. Minot, G. R., and Isaacs, R.: Lymphoblastoma (Malignant Lymphoma), J. A. M. A. **86**:1185 (April 17) and 1265 (April 24) 1926.

the patients with sclerosing lymphoma lived longer than those with the lymphoblastic form.

No attempt has been made to study the effect of roentgen treatment on the duration of this disease. In lymphatic leukemia in children, roentgen treatment seemed to have a detrimental effect and has been discontinued. Most of the adult patients have received this form of treatment,

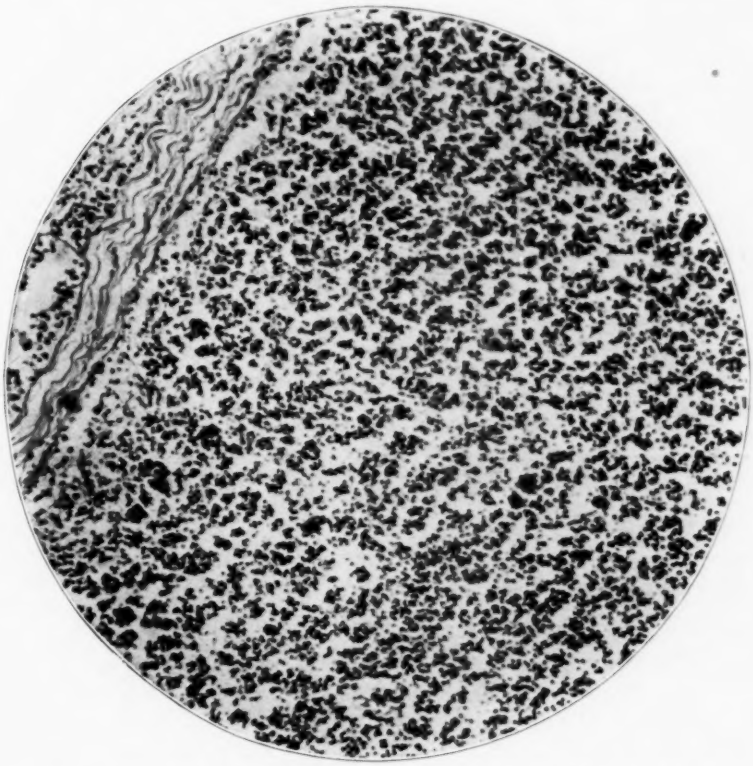

Fig. 4.—Lymphocytic type. The uniform small lymphocytes with little stroma, limited by the capsule of the node and a few trabeculae, give the appearance of a sac full of cells.

but so few have been given full doses at regular intervals, from beginning to end, that it seems unwise to draw general conclusions from a statistical study of this group. Aside from the possible influence on the length of life, roentgen treatment may be employed advantageously in certain cases to relieve pain, to prevent or delay the development of pleural effusion or ascites, or to improve the patient's general appearance.

An occasional instance of long duration may be noted in any form of lymphoma regardless of the type of treatment employed. Two patients with sclerosing lymphoma treated with the x-rays have remained quite comfortable for five and ten years, respectively. In three, in whom the cervical nodes were repeatedly removed surgically, the average duration was 6.6 years. In the latter group the enlarged nodes were

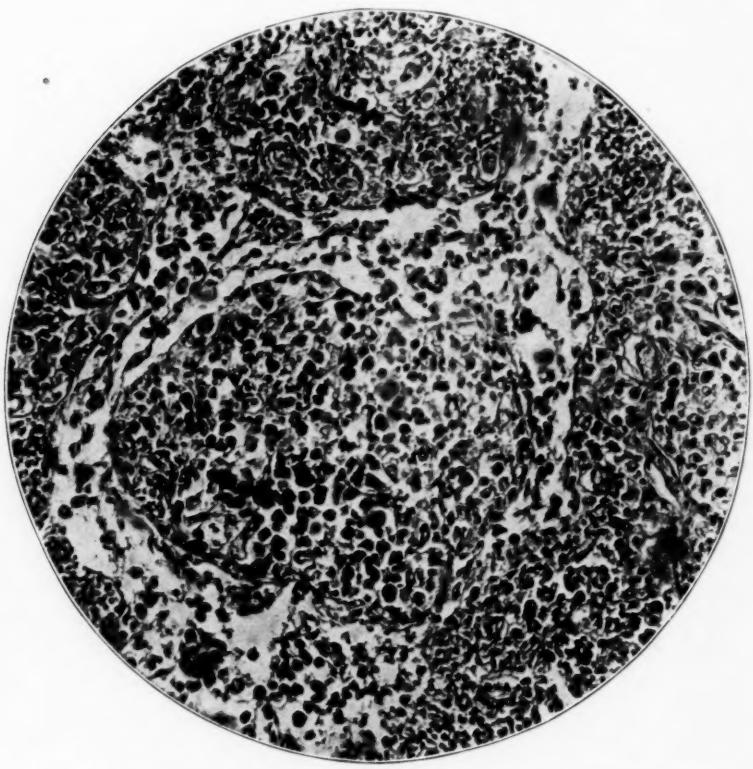

Fig. 5.—Lymphoblastic type. Cells which resemble those in a normal germinal center are scattered all through the node. There is more stroma than in the lymphocytic type but less than in the sclerosing type. Small lymphocytes are also present, and in places there are small pyknotic nuclei without recognizable cytoplasm.

confined for the most part to the neck, a form which may be very chronic. One patient with the lymphocytic type without leukemia lived eleven years and received no treatment for the first ten years of the illness.

Table 4 shows the incidence of involvement by lymph node groups as determined clinically, and table 5 is a similar tabulation from complete necropsy material.[5] Table 6 indicates the first enlargement noted by the patient.

While the involvement of the superficial nodes is readily detected, it is well recognized that relatively gross enlargement of the mediastinal and abdominal nodes and of the spleen frequently escapes clinical obser-

TABLE 4.—*Lymph Node Groups Found Enlarged Clinically*

	Cases	Cervical	Axillary	Inguinal	Mediastinal	Abdominal	Spleen
Sclerosing type	46	45	32	26	31	14	24
Endothelial type	2	2	2	..	1	1	..
Lymphoblastic type	19	19	15	13	11	12	10
Lymphocytic type							
With leukemia	55	52	50	48	33	31	46
Without leukemia	14	14	11	8	8	5	4
Unclassified	14	12	8	5	8	6	6
Totals	150	144	118	100	92	69	90

TABLE 5.—*Lymph Node Groups Found Enlarged at Necropsy*

	Cases	Cervical	Axillary	Inguinal	Mediastinal	Abdominal	Spleen
Sclerosing type	13	13	12	10	13	12	11
Endothelial type	1	1	1	..	1	..	..
Lymphoblastic type	5	5	4	4	4	5	4
Lymphocytic type							
With leukemia	17	17	16	15	15	16	16
Without leukemia	3	3	3	3	2	3	0

TABLE 6.—*Lymph Node Groups First Enlarged*

	Cases	Cervical	Axillary	Inguinal	Mediastinal	Abdominal	Spleen	Tonsil	Skin	Not Noted*
Sclerosing type	46	35	2	2	2	2	2	1	..	..
Endothelial type	2	2	..	..	..	..	..	..	..	..
Lymphoblastic type	19	14	..	2	1	..	..	2	..	..
Lymphocytic type										
With leukemia	55	32	..	4	1	3	6	..	1	8
Without leukemia	14	8	..	2	2	..	..	..	1	1
Total	136	91	2	10	6	5	8	3	2	9

* No enlargement noted by patient before examination, and several groups of nodes were found to be involved at the first examination.

vation (tables 4 and 5). In lymphatic leukemia there is an enlargement of nearly all the lymph node groups early in the course of the disease. In the noncirculating types, however, the involvement may remain limited until the later stages, when it usually becomes generalized.

Information as to the nodes first involved must be largely taken from the history (table 6). Patients readily detect enlargement of the cer-

5. Desjardins, A. U., and Ford, F. A.: Hodgkin's Disease and Lymphosarcoma, J. A. M. A. **81**:925 (Sept. 15) 1923.

vical nodes; they are less apt to notice inguinal adenopathy and rarely discover an involvement in the axilla. Abdominal nodes are nearly always massive before the subject is aware of their presence, and an increase in the size of those of the mediastinum is not suspected until after the appearance of pressure symptoms.

Table 7 represents an attempt to divide the types of fever occurring in the lymphomas into Pel-Ebstein and other varieties. Only fever occurring during the period of hospitalization is recorded, and an effort has been made to exclude all extraneous fevers. Instances of continued or remittent fever of 102 F. or above, lasting from three to thirty days and recurring after a period of apyrexia, are considered indicative of the Pel-Ebstein type of the disease, providing no infection is demonstrable. The second group includes irregular remittent and intermittent fevers without obvious infection, although some were continuous with terminal fevers and may not have been entirely the result of lymphoma. It is to be noted that the Pel-Ebstein fever is most common in the

TABLE 7.—*Incidence of Fever*

		Pel-Ebstein Fever		Prolonged Fever, Not Pel-Ebstein		Slight or No Fever
	Cases	Number	Per Cent	Number	Per Cent	
Sclerosing type	46	18	39	8	17	20
Endothelial type	2	..	..	1	50	1
Lymphoblastic type	19	3	15	4	21	12
Lymphocytic type						
With leukemia	55	1	1.8	26	47	28
Without leukemia	14	1	7	4	28	9
Total	136	23	16	43	31	70

sclerosing type; however, it is by no means limited to this variety of lymphoma.

In one case, the fever was sufficiently remarkable to warrant special mention. The patient had four periods of fever, each lasting about thirty days, ranging between 102 and 105 F., and separated by periods of apyrexia of from nine to eleven days. During most of the course, the spleen was the only part of the lymphatic apparatus that was demonstrably enlarged. The size of the spleen varied greatly and paralleled the temperature curve. It gradually enlarged as the fever increased until the lower margin reached the level of the umbilicus, and during each interval of apyrexia it receded to the costal margin. Two weeks before death there was a moderate enlargement of the cervical nodes, and a mass was demonstrated in the mediastinum by roentgen examination. At necropsy the abdominal nodes were enlarged, and metastatic lesions were found in the liver. The histologic picture was that of the sclerosing type of lymphoma.

Tables 8, 9, 10, 11 and 12 contain a summary of the blood manifestations in the various types of lymphoma.

TABLE 8.—*Leukocyte Count*

		Below 5,000	5 to 10 Thousand	10 to 15 Thousand	15 to 20 Thousand	20 to 25 Thousand	25 to 30 Thousand	30 to 35 Thousand	35 to 50 Thousand	50 to 75 Thousand	75 to 100 Thousand	100 to 200 Thousand	200 to 300 Thousand	300 to 400 Thousand	400 to 500 Thousand	500 to 600 Thousand	600 to 700 Thousand
Sclerosing type	High	5	12	13	6	6	1	2	1	..	..	..	..	..	..	..	..
	Low	8	17	10	6	4	1	..	..	..	..	..	..	..	..	..	..
Endothelial type	High	..	..	2	..	..	..	..	..	..	..	..	..	..	..	..	..
	Low	1	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Lymphoblastic type	High	3	9	5	2	..	..	..	..	..	..	..	..	..	..	..	..
	Low	6	12	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Lymphocytic type																	
With leukemia	High	2	4	2	4	5	1	3	7	7	3	8	3	4	..	1	1
	Low	9	7	6	8	6	3	3	2	4	2	3	..	1	..	..	1
Without leukemia	High	..	9	4	1	..	..	..	..	..	..	..	..	..	..	..	..
	Low	3	7	3	1	..	..	..	..	..	..	..	..	..	..	..	..

TABLE 9.—*Variation in Leukocyte Counts*

	Leukocyte Counts	
	Highest	Lowest
Sclerosing type	43,800	1,150
Endothelial type	14,000	4,500
Lymphoblastic type	17,500	2,400
Lymphocytic type with leukemia	600,000	600
Lymphocytic type without leukemia	15,800	4,000

TABLE 10.—*Differential Blood Counts*

	Neutrophilic Polymorphonuclears			Basophils Eosinophils			Endothelials			Lymphocytes		
	Average %	High %	Low %	Average %	High %	Low %	Average %	High %	Low %	Average %	High %	Low %
Sclerosing type	72.8	99	47	4.2	83	0	7.4	24	0	15.2	44	2
Endothelial type	78	82	74	2	4	0	21	24	22	2	4	0
Lymphoblastic type	70	95	40	1	6	0	7	17	0	25	56	4
Lymphocytic type												
With leukemia	10	48	0	0.1	4	0	0.4	10	0	89.5	100	52
Without leukemia	66	83	37	2	7	0	7	17	1	25	48	11

TABLE 11.—*Erythrocyte Counts*

		Millions									
		Below 1	1 to 1.5	1.5 to 2	2 to 2.5	2.5 to 3	3 to 3.5	3.5 to 4	4 to 4.5	4.5 to 5	Above 5
Sclerosing type	High	..	..	1	..	6	2	10	14	8	5
	Low	..	2	1	6	7	7	10	6	5	2
Endothelial type	High	..	..	..	..	..	..	..	2	..	..
	Low	..	..	..	1	..	1	..	..	..	..
Lymphoblastic type	High	..	..	..	1	..	..	5	5	8	..
	Low	..	..	2	1	2	3	13	16	2	..
Lymphocytic type											
With leukemia	High	1	5	3	5	1	8	9	11	7	5
	Low	4	8	3	8	4	10	7	6	4	1
Without leukemia	High	..	..	..	..	..	2	2	3	6	1
	Low	..	..	..	..	..	3	1	4	5	1

In table 8 the highest and lowest leukocyte values are recorded. It is to be noted that a leukocyte count of above 10,000 occurred in 63 per cent of the patients with the sclerosing type, in 37 per cent of those with the lymphoblastic type, in 89 per cent of the lymphocytic variety with leukemia, and in 35 per cent of those with lymphocytic lymphoma without leukemia. Counts of over 20,000 were obtained only in the sclerosing type and in lymphatic leukemia. In our experience, the sclerosing type of lymphoma is the most frequent cause for a nonleukemic leukocytosis of 20,000 per cubic millimeter, or above, in an afebrile patient. The leukocytosis of sclerosing lymphoma is likely to vary greatly from day to day. In 14 per cent of our patients with lymphatic leukemia the leukocyte count was never found to be above 15,000 per cubic millimeter. Leukocyte counts below 5,000 were fairly common in all types of lymphoma.[6] Our experience indicates that a pronounced leukopenia in lymphatic leukemia is a much more definite contraindication to roentgen therapy than a similar count in the noncirculating varieties.

TABLE 12.—*Terminal Anemia*

Type	Number of Cases	Average of Last Erythrocyte Counts in Millions
Sclerosing type	14	3.02
Endothelial type	1	2.36
Lymphoblastic type	6	3.06
Lymphocytic type with leukemia	17	2.04
Lymphocytic type without leukemia	3	3.76

The highest and the lowest individual leukocyte counts in each type are recorded in table 9. One patient with the sclerosing type of lymphoma had a leukocyte count of 43,800, 83 per cent of which were eosinophils.[7] In spite of such a marked leukocytosis, which was continuous in this patient, necropsy revealed no evidence of sepsis. The most pronounced leukopenia (600 per cubic millimeter) followed intensive roentgen treatment, which was given in a vain attempt to prevent strangulation by enlarged mediastinal and cervical nodes.

It is apparent from table 10 that no constantly abnormal differential count is found except in leukemia. Occasionally, high percentages of eosinophils or neutrophils are observed in the sclerosing type, and endothelial cells are often increased in all of the types. These abnormal differential counts and the extreme variability in the number of leukocytes are valuable diagnostic aids in some cases but are not constant.

6. Miller, H. R.: The Occurrence of Leukopenia in Hodgkin's Disease, Lymphogranuloma, Am. J. M. Sc. **173**:490, 1927.

7. Weber, F. P., and Bode, O.: Abdominal Lymphogranulomatosis Maligna (Hodgkin's Disease) with High Blood Eosinophilia and Lymphogranulomatous Infiltration of the Epidural Fat, Lancet **2**:806 (Oct. 15) 1927.

It will be noted that the lowest percentage of lymphocytes in lymphatic leukemia (53 per cent) approximated the highest percentage of lymphocytes in the lymphocytic type without leukemia (48 per cent). Differentiation between these two types was made on repeated leukocyte counts and differential studies. An occasional patient with the lymphocytic type without leukemia developed the blood manifestations of leukemia before death.

The severe grades of anemia were most common in the sclerosing type and in lymphatic leukemia (table 11). Almost complete replacement of the bone marrow by lymphomatous tissue was found in two cases of the sclerosing type in which the anemia was most marked. The anemia was of the secondary type except in those persons in whom the erythrocyte count was below 1 million, at which level anemia from any

TABLE 13.—*Diseases Associated with Lymphoma*

	Sclerosing Type	Endothelial Type	Lymphoblastic Type	Lymphocytic Type	
				With Leukemia	Without Leukemia
Number of cases	46	2	19	55	14
Tuberculosis					
Cervical nodes	1	..	..	..	1
Terminal miliary	1	..	..	..	2
Syphilis					
Latent	3	..	..	..	2
Aortic aneurysm	..	..	..	1	..
Erysipelas	..	..	..	2	..
Noma	..	..	..	2	..
Multiple sclerosis	..	..	..	1	..
Acute mania	..	..	..	1	..
Streptococcus peritonitis	..	..	..	1	1
Gout	..	..	..	1	..
Osteo-arthritis	..	..	..	1	..
Inguinal hernia	..	..	..	1	..
Carcinoma of the cheek	..	..	..	1	..
Hypertrophy of the prostate	..	..	..	1	..

cause usually has a color index of at least 1. Table 12 gives the erythrocyte counts in the various types of lymphoma shortly before death.

The diseases associated with the lymphomas in our series are indicated in table 13. Neither arteriosclerosis nor heart failure, both of which were common in the old men with leukemia, are included. In most instances, however, the cardiovascular changes were in keeping with the advanced age.

Tuberculosis occurred in only five cases, in three of which it was miliary. Each of the other two patients had numerous cervical scars from tuberculous adenitis during childhood. Active fibrocaseous tuberculosis of the lungs was not found in any of the cases in this series.

A diagnosis of syphilis was made in six cases. In five of these, there were no clinical manifestations of the disease. The Wassermann test, however, was strongly positive in all, and in four there was a history of chancre. The sixth patient had an aortic aneurysm and a positive Wassermann reaction.

Routine examinations of the blood have led to the diagnosis of lymphatic leukemia in patients admitted to the hospital for multiple sclerosis, osteo-arthritis, strangulated inguinal hernia, and hypertrophy of the prostate, and in a fifth with gout and a carcinoma of the cheek. In none of these cases were the lymph nodes large enough to arouse suspicion when the diagnosis was first made, and two have been observed for more than a year without the development of lymphadenopathy. Such observations would seem to indicate that the blood changes often antedate noticeable enlargement of the fixed lymphatic structures in leukemia. Erysipelas, noma, streptococcic peritonitis and miliary tuberculosis were the terminal infectious lesions seen in our series. Acute mania developed in one patient.

TABLE 14.—*Manifestations of Lymphoma Observed Clinically*

				Lymphocytic Type	
	Sclerosing	Endothelial	Lymphoblastic	With Leukemia	Without Leukemia
Number of cases	46	2	10	55	14
Pleural effusion	18	..	6	6	4
Pruritus	11	..	3	5	2
Infiltration of skin	3	..	2	3	1
Infiltration of breast	5	..	3	1	..
Infiltration of nasopharynx	1	1	3	..	1
Infiltration of stomach	..	..	1	..	..
Infiltration of intestine	1	..	..	1	1
Intestinal obstruction	1	..	..	1	1
Infiltration of bone	6	1	..	1	1
Involvement of vertebra with collapse and gibus	3	..	..	..	..
Involvement of nervous system	9	1	..	3	2
Herpes zoster	6	1	..	1	..
Horner's syndrome	1	1	..	..	1
Sudden deafness	2	..	..	1	..
Bronchial obstruction	4	..	..	..	..
Chylous ascites and chylothorax	..	..	..	..	1
Obstruction of ureter	..	..	..	1	1
Hematuria	..	..	..	..	1
Ulcer of penis	..	..	..	2	..
Acute arthritis	..	..	..	13	..
Subcutaneous emphysema	1	..	..	..	..

Although the primary lesion in all types of lymphoma is no doubt in the fixed lymphatic tissue, secondary manifestations may be met with in any of the body structures. The pathologic histology is the same in the lymph nodes and in the metastatic nodules. The clinical manifestations, however, are protean and are dependent on the tissue predominantly involved (table 14).

Pleural effusion was observed in 39 per cent of patients with the sclerosing type and in 23 per cent of the whole group. This particular complication occurs so frequently that it should be anticipated and an attempt made to delay its development by roentgen treatment of the mediastinal nodes. Effusions were more frequently induced by encroachment on the great veins or by obstruction of lymphatics than by metastases or infiltration in the pleura.

Pruritus[8] has long been recognized as a frequent manifestation in the sclerosing type, but it was also present in the other types in our series. We have not recognized a characteristic type of nonmetastatic skin lesion. In most cases of pruritus, long continued scratching had led to abrasions and consequent inflammatory thickening of the skin. The itching skin without local lesions was usually dry and rough.

Fig. 6.—The diffuse flat skin lesions of the sclerosing type. Enlarged inguinal lymph nodes can also be seen.

Infiltration of the skin with the formation of definite nodules was considerably less common than pruritus but occurred in all types. In the sclerosing type the nodules were flat, elevated 1 to 2 mm. above the surface, and measured from 1 mm. to 3 cm. in diameter (fig. 6). Hyperemia was confined to the lesions, and the involved skin was scaly. These lesions were definitely in the dermis and moved freely over the subcuta-

8. Miller, H. E.: Lymphogranulomatosis Cutis, Hodgkin's Disease, Arch. Dermat. **17**:156 (Feb.) 1928.

neous tissue. One of the patients with the lymphoblastic type presented innumerable bluish, globular tumors in the skin, the largest of which was less than 1 cm. in diameter. Massive leukemic infiltration of the skin, such as has been repeatedly described in the literature, occurred in one patient in our series. Extensive infiltration was present in the skin of the arms, chest, abdomen, back and legs. There was a diffuse involvement over the back and chest which gave the skin a bronze color and a leathery consistency. In many places there was distinct tumor formation. The largest of these was 10 cm. in diameter and extended 5 cm. above the surrounding skin. The surfaces of the tumors were fissured

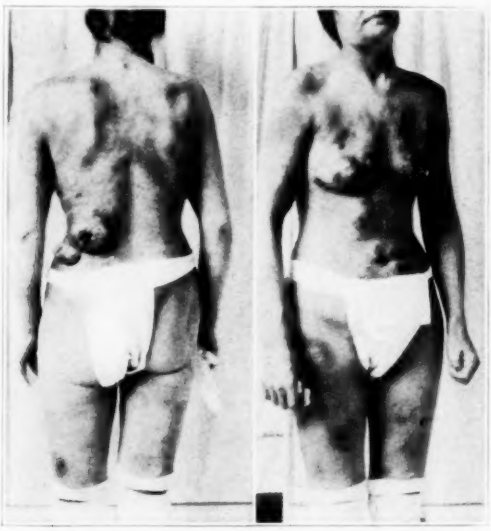

Fig. 7.—The diffuse brawny induration of the skin over the back with two large weeping tumors. The front view shows tumors in all stages of development.

and were covered by a thick layer of dried exudate. Serum oozed from the fissured surfaces of some of the tumors, especially those beneath the breasts and in the groins (fig. 7). The involvement of the skin observed in the other cases of lymphatic leukemia and in the one of lymphocytic type without leukemia was not nearly so extensive. No instances of universal leukemia cutis were encountered in our series.

Tumors of the breast were found in nearly all types of lymphoma. Unfortunately, histologic examination of the lesions of the breast was not made. One of the tumors had the gross characteristics of carcinoma in that the nipple was retracted and fixed, there was a "pig skin" appearance about the nipple, and the only palpably enlarged lymph nodes were

in the corresponding axilla. Three of the patients were males and six were females. In the males there was involvement of the entire breast, while in the females the infiltration was localized and formed nodules. All of the lesions of the breast responded promptly to roentgen treatment.

Infiltration of the nasopharynx is often considered a characteristic feature of the lymphoblastic type (lymphosarcoma). The six cases in our series with such involvement represented four different types of lymphoma.

Infiltration of the gastro-intestinal tract [9] by the various types of lymphoma has been reported frequently in recent years. In some instances, the lesion has apparently been limited to the stomach or bowel. The condition has been reported as "round cell sarcoma" or "lymphogranuloma." Gross gastric infiltration was found only once in our series. The case was that of a woman, aged 31, in whom there was also an involvement of the bowel, the cervical and abdominal nodes and the spleen. Lymphoblastic tumor tissue varying from 1 to 2.5 cm. in thickness involved most of the stomach wall. Roentgen examination of the gastro-intestinal tract was made of many of the patients of this series, but no other instance of gross involvement was recognized.

Unless it is extensive, involvement of the bowel in any form other than the sclerosing type is difficult to diagnose even histologically, because of the large amount of lymphoid tissue normally present. In the three cases recorded there were definite symptoms of involvement of the bowel and marked and unquestionable overgrowth of lymphoid tissue was demonstrated, once by proctoscopic examination and twice at necropsy. This group was distinct from those in which intestinal obstruction occurred.

The intestinal obstruction which occurred in three different types was chronic and progressive. In each of the cases it resulted from encroachment on the small bowel by enlarged mesenteric and retroperitoneal nodes. The nature of the condition was appreciated clinically in all cases by inference from involvement of lymph nodes elsewhere.

In the involvement of bone, lymphomas present one of their most interesting features. We have seen metastases mistaken roentgenologically for both pyogenic and tuberculous osteomyelitis. Destruction of part of the ischium without any sign of proliferative reaction was seen in one case (fig. 8*A*). Following roentgen treatment new bone was laid down, and a satisfactory functional result was obtained (fig. 8*B*). In three cases in which there was vertebral involvement (fig. 9), with the formation of angular kyphosis, the roentgenograms were prac-

9. Hayden, H. C., and Apfelback, C. W.: Gastro-Intestinal Lymphogranulomatosis, Arch. Path **4**:743 (Nov.) 1927.

tically identical with those of tuberculosis of the spine.[10] One of these patients was given roentgen treatment over the involved vertebra with little or no change in the appearance of the lesion. Laminectomy was done later in an attempt to relieve myelitis, and material removed from the diseased vertebra showed bone invaded by a tumor which had the characteristic structure and formation of the sclerosing type of lymphoma. One case of leukemia came under observation after an operation for pyogenic osteomyelitis of the left femur (fig. 10). The diagnosis had been made by the x-rays. No pus had been found at operation, and necropsy later showed many large lymphoid nodules in the bone marrow.

Organic lesions of the nervous system due to lymphoma are considered frequent by some observers,[11] but most discussions of the condition in textbooks fail to mention nervous lesions of any type.

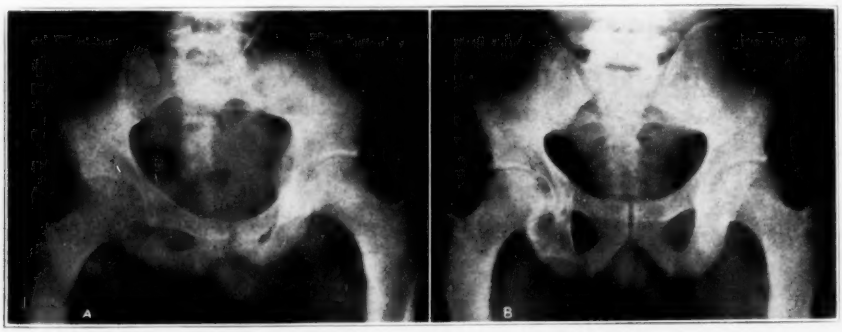

Fig. 8.—In *A*, the absence of part of the descending ramus of the ischium can best be appreciated by stereoscopic study, but a comparison with *B*, which is the same pelvis after irradiation, will give an idea of the extent of the lesion. In *B*, roentgen evidence of formation of new bone started promptly after irradiation and continued until a good functional result was obtained.

The relationship between herpes zoster [12] and lymphoma is not clear. The six instances of herpes zoster which occurred among the forty-six cases of the sclerosing type of lymphoma would not be likely to be purely coincidental. In one patient the herpes zoster developed over the distribution of the fourth right thoracic nerve and was followed in about three months by a collapse of the body of the fourth dorsal

10. Robin, N. H.: An Unusual Metastatic Manifestation of Hodgkin's granuloma, Am. J. Roentgenol. **14**:251, 1925.

11. Ginsburg, S.: Hodgkin's Disease, with Predominant Localization in Nervous System, Early Diagnosis and Radiotherapy, Arch. Int. Med. **39**:571 (April) 1927.

12. Pancoast, H. K., and Pendergrass, E. P.: The Occurrence of Herpes Zoster in Hodgkin's Disease, Am. J. M. Sc. **168**:326, 1924.

vertebra occasioned by a metastatic lesion. In another the herpes developed shortly before death, and the dorsal root ganglions and vertebra were examined at necropsy, but no gross evidence of metastases was discovered. In other cases postmortem examination was not possible, but there was no gross evidence of metastatic lesions in the spine or along the course of the involved nerves.

Horner's syndrome was not found frequently in our series in spite of the large percentage of cases showing involvement of the cervical nodes. In all three instances, the condition was unilateral. The syndrome comprises enophthalmos, a slight droop of the upper lid, myosis which is indifferent to cocaine and unilateral hyperhidrosis, all of which

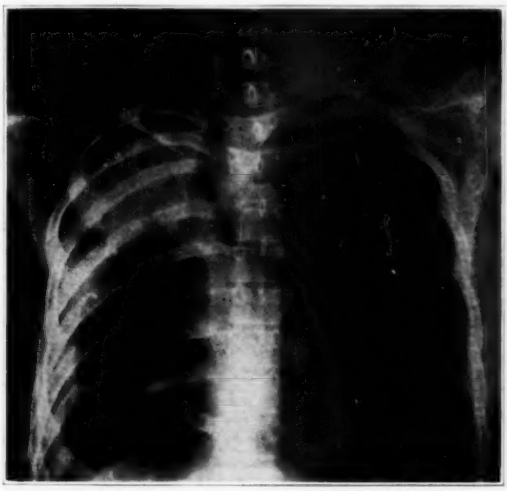

Fig. 9.—Collapse of the fourth dorsal vertebra and opacity of the right lung.

may be the result of paralysis of the cervical sympathetics. The elasticity of the enlarged nodes and the fact that the tumor shows little tendency to invade perilymphatic tissue are the chief reasons for the rarity of pressure paralysis in lymphoma.

Sudden deafness has occurred in some of our patients with disease of the hematopoietic system. In most instances, it has appeared in association with bleeding from the mucous membranes or hemorrhages into the skin. Although the pathologic basis was never established, it was assumed that such deafness was in some way induced by hemorrhage.

Lesions of the nervous system not falling in any of the foregoing groups have apparently been produced by encroachment rather than actual invasion or metastases. Myelitis and paralysis of part of the

brachial plexus, of the sixth nerve, of the eleventh nerve, of the vagus and of a part of the lumbosacral plexus were noted in our series. Hemiplegia developed in a child of 5 years with leukemia. The exact cause was not determined.

In two patients the major complaint was pain, in one extending down the legs and in the other encircling the lower part of the abdomen. Neither of these patients showed loss of sensation nor change in the reflexes. They were not included in the group showing organic nervous lesions, although root pain was considered the most plausible explanation for the symptoms. Another patient with a metastasis in the ischium had pain much like that in sciatica.

Partial bronchial obstruction was seen in four cases of the sclerosing type. In each, the respiratory difficulty was due to a mediastinal tumor. The symptomatology strikingly resembled that of bronchial asthma.

Chylous ascites and chylothorax occurred in one instance in which a solid mass of enlarged nodes extended from the left cervical region into the left axilla. Hydronephrosis from partial obstruction of the left ureter was discovered in two cases at necropsy. A gross and persistent hematuria appeared in one patient. Cystoscopic examination showed bloody urine coming from both ureters. The pyelograms were normal. Two old men with leukemia developed ulcers of the penis while under observation. In each, the ulcer was indurated and painless. Both were repeatedly examined for spirochaeta pallida, but the results were negative. In one, a biopsy revealed only closely packed lymphoid cells.

Acute arthritis occurred in thirteen of the twenty patients with lymphatic leukemia under 21 years of age.

Subcutaneous emphysema extending from the zygoma to the shoulder was observed in a boy, aged 6 years, with the sclerosing type of lymphoma. The cervical nodes were enlarged, but there was no roentgen evidence of metastatic lesions in the lungs.

Table 15 was compiled for the purpose of conveying some idea of the widespread pathologic changes in the various types of lymphoma. In all of the cases there was an involvement of some of the lymph nodes, and in a vast majority there was a significant increase in weight of the spleen, and histologic changes were demonstrated. Involvement of other organs and tissues varied somewhat as to frequency and as to the nature of the lesions in the different types. In the sclerosing and endothelial types the lesions, apart from those of the fixed lymphatic tissue, were in the nature of discrete nodules. Organs in which there was an infiltration of only a few lymphocytes were not considered to be involved. The term metastasis seemed appropriate for such discrete nodules. The recognized metastases were nearly all gross; some were rounded with well defined borders, while others were invasive with irregular margins, but all showed the same histologic structure as the

lymph nodes. Some of the lesions of the lymphoblastic type were discrete nodules with localized destruction of the parenchyma of the involved organ, while others were more in the nature of an infiltration, with lymphoid cells surrounding the vessels or arranged in rows between the parenchymatous elements of the involved organ. In the lymphocytic type, both with and without leukemia, either perivascular or intercellular infiltration of lymphoid cells was common, while the formation of distinct nodules was correspondingly uncommon.

Leukemic infiltration of some degree was found in all cases of lymphatic leukemia, and its extent more nearly paralleled the duration

TABLE 15.—*Tissues Showing Involvement Microscopically*

	Sclerosing Type		Endothelial Type		Lymphoblastic Type		Lymphocytic Type: With Leukemia		Lymphocytic Type: Without Leukemia	
	A*	B†	A	B	A	B	A	B	A	B
Lymph nodes	15	15	1	1	5	5	19	19	2	2
Spleen	15	12	1	0	5	3	19	19	2	1
Bone marrow	4	1	1	1	1	1	10	10	1	0
Liver	14	4	1	1	5	3	17	17	2	2
Kidney	15	3	1	0	4	1	17	15	2	1
Suprarenal	11	1	1	0	2	2	14	6	2	2
Heart	13	0	1	0	4	1	13	5	2	1
Pericardium	5	3	..	..	2	1	9	4	1	1
Adventitia of aorta	6	9	1	0	1	0	9	2	..	..
Lungs	14	7	1	1	4	2	14	10	1	0
Stomach	..	..	..	..	2	1	2	1	..	..
Intestine	2	1	..	..	2	1	7	4	..	..
Pancreas	12	2	1	0	4	3	13	2	2	2
Gallbladder	..	..	..	..	1	1	2	1	..	..
Peritoneal fat	..	..	..	..	1	1	3	3	..	..
Prostate	2	0	1	0	1	0	6	4	1	0
Bladder	2	0	1	0	..	..	6	6	..	..
Ureter	..	..	..	..	..	..	1	1	..	..
Uterus	1	0	..	..	..	..	1	1	..	..
Thyroid	4	1	..	..	..	..	..	..	..	..
Thymus	..	..	..	..	..	..	2	2	..	..
Skin	1	0	..	..	1	1	1	1	1	1
Bone	2	2	1	1	..	..	1	1	..	..
Conjunctiva	..	..	..	..	..	..	1	1	..	..
Peritoneum	..	..	..	..	..	..	2	2	..	..

* A indicates number of cases in which histologic sections of the indicated organs were available for our study (cases seen at necropsy only).
† B indicates number of instances in which infiltration or metastases were found.

than any other single feature. Lymphatic leukemia in childhood was rapidly fatal, frequently with hemorrhages of the skin and mucous membrane and high fever, whereas in adults it was essentially a chronic disease lasting about three years and not accompanied by hemorrhages except terminally. Yet the pathologic changes in these two conditions varied only slightly. The cells making up the enlarged lymphoid structures in children were larger, on an average, and often appeared more immature than those of lymph nodes in adult lymphatic leukemia. The difference in the fixed lymphatic cells of leukemia in the child and the adult was no greater than that seen when the lymphocytes of the normal blood smear of a child are compared with those of an adult. Regardless of age the viscera were usually less extensively infiltrated in the cases of short duration than in those of years' standing.

It is at once apparent from the table that a great variety of organs and tissues was involved in our series. In complete necropsies the abdominal and thoracic viscera were sectioned, and in addition sections were taken from other tissue which showed evidence of gross pathologic change. Some of the older necropsies were not complete, and a few of the sections that were unsatisfactory were discarded. Definite metastases are readily recognized in the gross so that the figures for the sclerosing and endothelial types are probably quite accurate, even though some of the organs were not sectioned for histologic study. The gross evidence is not so reliable in leukemia. It seems quite likely

Fig. 10.—There is a punched-out appearance in the neck and upper shaft of the left femur. The site of an operation for osteomyelitis can be seen at a lower level.

that leukemic infiltration is almost universal in long-standing cases, and if more organs were sectioned more infiltration would be found. We have found lymphoid infiltration microscopically in chance sections from the bladder, peritoneum, peritoneal fat and uterus. In one instance, a leukemic infiltration of the conjunctiva was demonstrated (fig. 11). Leukemic involvement of this structure has been reported in the literature.[13] The pancreas and heart seemed to be relatively immune,

13. Meller, J.: Die lymphomatosen Geschwulstbildungen in der Orbita und im Auge, Arch. f. Ophth. **62**:130, 1905.

and the most marked infiltrative lesions were observed around the portal veins and between the kidney tubules.

It is worthy of special mention that 50 per cent of the lungs examined from patients with the sclerosing type of lymphoma showed definite metastases.

DISEASES SIMULATED BY LYMPHOMA

Dermatitis.[13]—The danger of overlooking lymphoma in a patient complaining of itching has been stressed repeatedly. The firm, elastic, freely movable, nontender nodes of lymphoma are in distinct contrast to the soft, tender nodes resulting from the drainage of acute skin lesions or the fibrous, shrunken, and anchored nodes of ancient infection. Irrespective of whether or not the skin lesions were the result of scratching or metastases to the skin, the nodes were sufficiently characteristic in all of our cases to establish the diagnosis without difficulty.

Mycosis Fungoides.[14]—In lymphatic leukemia large, warty skin lesions may occur which grossly are not distinguishable from the lesions of mycosis fungoides (fig. 12). Indeed, there is considerable discussion among dermatologists as to

Fig. 11.—Boggy masses of lymphoid infiltration in the conjunctiva in lymphatic leukemia.

whether or not these conditions are identical. We have had two cases in which the lesions were grossly similar. In one case the histologic composition of the enlarged lymph nodes and of the skin tumors was that of the lymphocytic type of lymphoma, and the blood manifestations were those of lymphatic leukemia, while in the other the lymph nodes were not enlarged, the blood was normal, and the histologic manifestations of the skin tumors were those of granulation tissue and inflammatory cells (fig. 13).

Tumors of the Breast.—Most of the lesions of the breast occurring in patients with lymphoma resemble mastitis more than carcinoma. If one appreciates the fact that involvement of the breast occurs in lymphoma, there will usually be little difficulty in diagnosis. However, the diagnosis may be largely a matter of inference from enlarged lymph nodes elsewhere because of the notorious difficulty in determining the characteristics of a small tumor in a large breast. In one of our patients, a woman, aged 63, the condition was promptly diagnosed carcinoma of the breast by an able surgeon. The right breast was edematous, with the

14. Highman, W. J.: Mycosis Fungoides and Kindred Conditions; the Criteria of Their Diagnosis, Arch. Dermat. & Syph. **13**:522 (April) 1926.

"pig skin" appearance about the areola, a retracted nipple, and a 3 cm. mass of hard lymph nodes in the right axilla. The abdomen was distended with fluid, and a mass could be felt in the left upper quadrant. The only palpable lymph nodes were in the right axilla, but there was a history of a node having been removed from the left cervical region six months before. The microscopic diagnosis, which we were able to confirm, was the lymphoblastic type of lymphoma. Irradiation caused a prompt decrease in the size of the axillary nodes; the edema disappeared from the breast, the skin became normal and the nipple freely movable.

Fig. 12.—Mycosis fungoides. The resemblance to leukemic infiltration as shown in figure 7 should be noted.

Without the previous biopsy, we would certainly have concurred in the diagnosis of carcinoma of the breast.

Tumor of the Spinal Cord.—Symptoms of myelitis occurred in one of our cases but were associated with a definite metastatic lesion of the vertebral body at the corresponding level, and a tumor of the spinal cord was therefore not considered. The diagnosis of a tumor of the cord was, however, considered in two other cases in which there was excruciating pain. In one the pain extended down the legs, and in the other it encircled the lower part of the abdomen. The signs of myelitis did not develop in either patient.

Paroxysmal Tachycardia.—In one case, which was reported in detail by Dr. V. C. Graber,[15] a nodal paroxysmal tachycardia developed, and necropsy showed that the vagi were compressed by enlarged mediastinal lymph nodes. There was marked myelin degeneration of both vagi and especially of those branches entering into the cardiac plexus.

Carcinoma of the Stomach.[16]—Two elderly men with lymphatic leukemia were sent to the hospital with the diagnosis of carcinoma of the stomach. Such errors

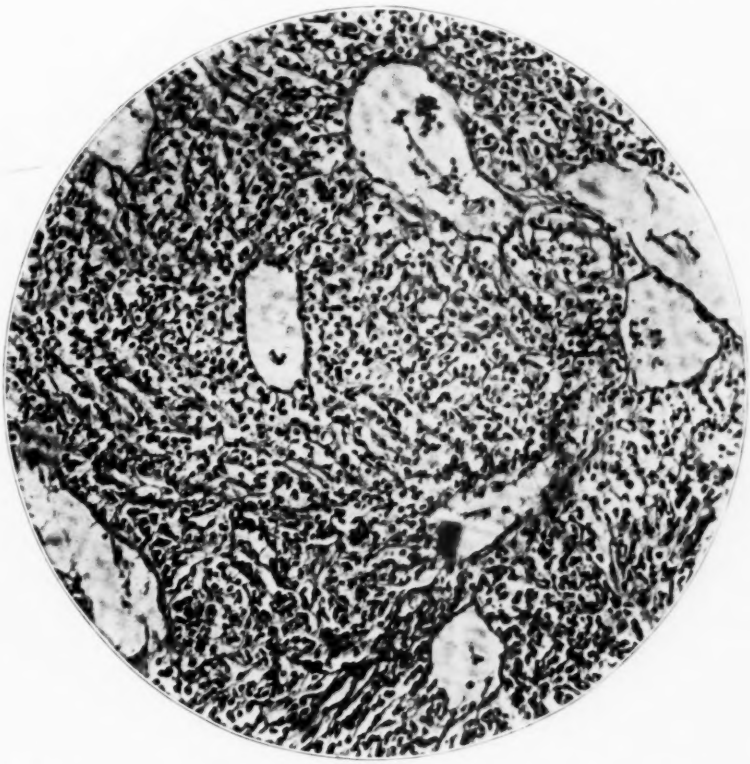

Fig. 13.—Granulomatous tissue making up the nodules in mycosis fungoides.

may be easily avoided by examining the blood or by a roentgen study of the stomach. The similarity between lymphatic leukemia and carcinoma of the

15. Graber, V. C.: Paroxysms of Tachycardia Occurring in Case of Hodgkin's Disease in Which Vagus Nerves Were Degenerated by Pressure of Enlarged Mediastinal Glands, Am. Heart J. **1**:564, 1926.

16. Holmes, G. W.; Dresser, R., and Camp, J. D.: Lymphoblastoma (Malignant Lymphoma); Its Gastric Manifestations with Special Reference to Roentgen Findings, Radiology **7**:44, 1926.

stomach is really superficial. When there is an actual invasion of the stomach wall, however, by one of the noncirculating types, the correct clinical diagnosis may be established only by the discovery of an involvement of the peripheral lymph nodes. Such circumstances obtained in one of our cases of the lymphoblastic type. The stomach was diffusely involved, and the cervical nodes were enlarged on both sides. These nodes were, however, too extensively involved to be confused with the ordinary "Virchow gland." Without involvement of the peripheral lymph nodes, the differentiation is apt to be impossible clinically.

Carcinoma of the Bowel.—One of our patients passed enormous amounts of slightly changed blood in the stool. There was a large irregular mass filling most of the left half of the abdomen, and the patient gave a history of obstinate constipation. The diagnosis happened to be easy, because the blood manifestations were those of leukemia and all of the peripheral lymph nodes were enlarged. In another patient, there were multiple lymphoid tumors of the bowel wall with ulceration of the mucosa over them.

Colitis.—One patient was sent to the hospital with a diagnosis of colitis. There was almost continuous diarrhea for eight months and a loss of 60 pounds (27.2 Kg.) in weight. The stools contained considerable fat but little mucus. There had been several frank hemorrhages. Examination revealed infiltrative lesions of the skin and enlarged lymph nodes in the inguinal regions and in the neck. The histologic structure of an excised inguinal node was that of the sclerosing type of lymphoma. Irradiation had no appreciable effect on the diarrhea. At necropsy, there was a uniform enlargement of the lymph nodes in the mesentery. There were no collections of fat in the lymphatics of the bowel wall, but the patient's diet had been largely carbohydrate for weeks before death, and he had eaten little during the last several days of life. The bowel wall showed no gross evidence of metastasis. A few small mucous cysts were noted in the submucosa. It is believed that the enlarged mesenteric nodes obstructed the flow of fat in the lymph channels and thereby induced the marked emaciation and possibly the diarrhea.

In another patient with the symptoms of colitis, an extensive increase of the lymphoid tissue of the bowel was seen by the proctoscope. The enlarged lymph follicles had the appearance of papillomas.

Osteomyelitis.—One of our patients had been operated on elsewhere for pyogenic osteomyelitis. A blood count would have prevented the error. Roentgen examination showed a disturbance in the medullary portion of the left femur.

Tuberculosis of the Spine.[13]—The diagnosis of tuberculosis of the vertebral bodies was made by the roentgenologist in three of our patients with the sclerosing type of lymphoma. In the one who came to necropsy, a metastatic lesion was found responsible for the destruction of the vertebra. In another, the diagnosis was established by a biopsy. The lesion in the third was assumed to be that of lymphoma on the basis of the observations elsewhere and in the absence of clinical manifestations of tuberculosis.

Tuberculosis of the Lungs.—Four patients in our series were sent to us from sanatoriums for the treatment of tuberculosis. In all, the condition was originally diagnosed tuberculosis. The lungs were frequently invaded by metastatic lesions (50 per cent of our fourteen necropsies) in the sclerosing type of lymphoma. The clinical resemblance to tuberculosis may be striking. In one of the patients with collapse of a vertebral body, there was an extensive involvement of the right lung. There was no expansion of the right side of the chest; the percussion note was flat, and the breath sounds were faint and tubular (fig. 14*A*). A needle was inserted and a solid lung encountered but no fluid obtained. However, there were

no rales, no evidence of cavitation, no sputum, and no history to suggest pulmonary tuberculosis. So extensive a tuberculous pneumonia could hardly have occurred without the patient's knowledge. On the basis of the foregoing observations, we felt that tuberculosis could be excluded in spite of a solid lung and a roentgen diagnosis of tuberculosis of the spine, and later developments have proved this assumption to be correct at least so far as the vertebral involvement is concerned.

Tuberculosis of the Peritoneum.—In one patient a diagnosis of tuberculous peritonitis was made on the bases of a loss of 25 pounds (11.3 Kg.) in weight, abdominal discomfort, an irregular fever, sweats and ascites. An enlarged lymph node was removed at operation which showed the histologic picture of the sclerosing type of lymphoma. There was no enlargement of the peripheral nodes.

Serofibrinous Pleurisy.—Pleural effusions are common in all types of lymphoma, but usually there is sufficient adenopathy to prevent errors in diagnosis. One of our patients gave a history of having had a thoracentesis and stated that tubercle bacilli were found in the aspirated fluid. A diagnosis of lymphoma seemed quite

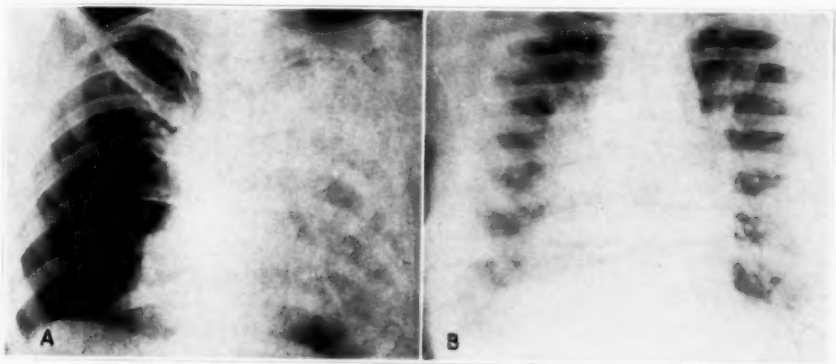

Fig. 14.—*A*, the sclerosing type of lymphoma involving the right lung. *B*, involvement of the mediastinal lymph nodes with encroachment on the trachea or bronchi to produce asthma-like symptoms.

obvious because of many enlarged nodes in the neck. A biopsy was done, however, to remove all doubt, and the sclerosing type of lymphoma was discovered. No evidence of tuberculosis of either the lung or the pleura was found at necropsy five months later.

Bronchial Asthma.—The diagnosis of bronchial asthma was made in four of the patients in our series. In all, there was an involvement of the peribronchial lymph nodes early in the course of the disease. Each had the sclerosing type of lymphoma and later had a generalized adenopathy. One of these patients is worthy of brief mention because of the striking resemblance of the clinical picture to that of bronchial asthma. She gave a history of having had hay-fever for years. A short time prior to admission to the hospital, attacks of nocturnal dyspnea began to appear which were accompanied by cough and the expectoration of frothy sputum. During the attacks, sibilant and sonorous rales were heard throughout both lungs. Because the attacks were not relieved by epinephrine, a roentgen examination of the chest was made (fig. 14 *B*), and an enlargement of the hilum nodes was discovered.

Rheumatic Fever.—It is of interest to note that 65 per cent of the patients with lymphatic leukemia under 21 years of age had acute symptoms of involvement of the joints. This feature was not observed in the older patients with lymphatic leukemia, nor was it noted in the other forms of lymphoma. Neither the cause nor the nature of the joint manifestations is understood. In one case the synovial membrane was examined histologically at necropsy about three months after the onset of acute symptoms, and no pathologic change was found. Histologic examination was not made in the other cases, and none of the joints was aspirated. It was assumed that hemorrhage was the most likely cause for the swelling, redness, effusion and pain in such joints. The involvement in nearly all cases was multiple and shifted from joint to joint much like rheumatic fever. In one case there was a marked anemia and a loud hemic heart murmur, but no valvular disease was found at necropsy. In a number of instances, the diagnosis of rheumatic fever was made prior to the admission to the hospital.

Still's Disease.—Still's disease is simulated by those cases of lymphatic leukemia in childhood in which the joint symptoms last for a considerable period and in which the enlargement of the spleen and the lymph nodes is only moderate. We have seen such an error made on one occasion.

Primary Syphilis.—A leukemic infiltration of the glans penis leading to the formation of an indolent ulcer is a rather unique observation which is difficult to explain, especially in the absence of other infiltration of the skin or mucous membrane. Priapism was not present in either case.

Hemolytic Icterus.—One of our patients, a young man, aged 24, complained of attacks of abdominal distress, which had appeared at intervals for four years. The attacks came on gradually with a feeling of indisposition and anorexia followed by nausea and, at times, vomiting. Pain and tenderness were noted under the right costal margin and a feeling of fulness in the corresponding location on the left side. A slight jaundice would appear in forty-eight hours and gradually disappear after a week. After two or three weeks the appetite would return, and the patient would consider himself well. At first these attacks came once a year but later occurred every few months. When first examined, the spleen was somewhat tender and extended to the level of the umbilicus. The tenderness was particularly noted during the attacks. The liver was enlarged and also tender during the attacks. There were five large lymph nodes in the left axilla, the largest measuring 4 cm. in diameter. These nodes were observed to increase in size during periods of abdominal distress. Repeated tests failed to show increased fragility of the erythrocytes. The histologic examination of an excised node established the diagnosis of the sclerosing type of lymphoma. The patient died outside the hospital and, unfortunately, a necropsy was not obtained.

Aplastic Anemia.—A woman, aged 58 years, with an enlarged spleen and a severe aplastic anemia of unknown etiology was kept alive for two months by transfusions. Six days before her death she developed greatly enlarged nodes in the cervical, axillary and inguinal regions. A diagnosis of lymphoma (sclerosing type) was apparent when the enlarged nodes appeared, and this was confirmed at necropsy. The erythrocyte counts ranged from 1,800,000 to 1,010,000; hemoglobin, from 29 to 19 per cent; leukocytes, from 3,700 to 2,200; and the hematocrit, from 13 to 10 per cent. Polymorphonuclear neutrophils were as high as 64 per cent after transfusion and as low as 42 per cent at other times. There was a greatly reduced platelet count, and the thrombocytocrit value varied between 0.10 and 0.15 per cent (normal, from 0.4 to 0.6 per cent). The reticulocytes varied between 1.3 and 0.1 per cent, and there were no nucleated erythrocytes.

At necropsy, the bone marrow was almost completely replaced by tissue showing the histologic characteristics of the sclerosing type of lymphoma.

Hypernephroma.—A persistent hematuria and enlarged cervical lymph nodes in one case led us to suspect a hypernephroma with metastases. A node was removed which showed the histologic picture of lymphoma of the lymphocytic type. The pyelograms of both kidneys were normal. The lymphocytic type of lymphoma in our series has rarely been associated with discrete nodules in the parenchymatous organs. Whether or not the infiltration of lymphoid cells between the kidney tubules could induce an extensive hematuria is a matter for speculation. The bleeding was not affected by irradiation, and the patient has not come to necropsy.

Malta Fever.—When a patient has a fever of from 102 to 105 F. for thirty days, with an enlarged spleen as the only abnormal physical manifestation, and a marked leukopenia, there are many possibilities to be considered in diagnosis. If, as occurred in one of our cases, such a bout of fever repeats itself four times, the possibilities are reduced to lymphoma, undulant fever, and perhaps kala-azar. Blood cultures and agglutination tests excluded typhoid and undulant fever. Kala-azar has never been reported in a permanent resident of the central United States. In retrospect, the diagnosis of lymphoma should have been easy. Biopsy, however, was not possible, and we were aware of having made a diagnosis of the splenic type of lymphoma in two similar patients in the past, both of whom recovered. The former cases were probably unrecognized instances of undulant fever.

COMMENT

In the foregoing series of 150 consecutive cases of lymphoma, the clinical manifestations were protean and were dependent on the involvement of many anatomic structures. The great range of the clinical varieties was a striking feature. It would therefore seem that the prevailing conception regarding the usual manifestations of lymphoma has been taken from the rather brief discussions of the disease appearing in textbooks.

Many of the most marked variations in course and clinical manifestations occurred in patients with the same basic pathologic change. From this study, it would appear that the popular division of lymphatic leukemia into acute and chronic forms gives an exaggerated idea of the basic differences between the two. As in diabetes mellitus, we may be dealing with a disease that is borne much better by the adult than by the child.

A marked clinical variation without corresponding qualitative changes in the basic pathologic histology was also seen in the "acute" and "chronic" cases of the sclerosing type of lymphoma. Here, again, the acuity of the disease tended to have an inverse relation to the age.

The clinical manifestations of the sclerosing, endothelial, lymphoblastic and the lymphocytic type without leukemia may be practically identical.

The conditions discussed in this communication may or may not eventually prove to be a variation of the same disease entity. They

differ in respect to the condition of the circulating blood, the type of cell predominating in the enlarged lymphoid structures, and to a certain extent, in the type of lesion produced in the viscera. In other respects, there is a striking similarity. All primarily involve the fixed lymphatic structures and terminate fatally. Fever of an almost specific variety may occur in any type. In all there may be a secondary involvement of skin, bones, nervous tissue, breast and viscera. The basic metabolic rate is often increased in all types. The histologic variation in the various types of lymphoma is no greater than that seen in carcinoma of the stomach.

THE USE OF EPINEPHRINE AS A DIAGNOSTIC TEST FOR ANGINA PECTORIS

WITH OBSERVATIONS ON THE ELECTROCARDIOGRAPHIC CHANGES FOLLOWING INJECTIONS OF EPINEPHRINE INTO NORMAL SUBJECTS AND INTO PATIENTS WITH ANGINA PECTORIS *

SAMUEL A. LEVINE, M.D.

A. CARLTON ERNSTENE, M.D.

AND

BERNARD M. JACOBSON, M.D.

BOSTON

Some years ago one of us (S. A. L.) was called to see a patient with angina pectoris who was at that time experiencing a severe attack of bronchial asthma. Epinephrine, 0.5 cc., was administered subcutaneously, and after several minutes the patient developed an attack of severe anginal pain. Some time later, O'Hare,[1] in studying the effect of various drugs on arterial hypertension, observed that epinephrine produced a seizure of typical anginal pain in a patient with angina pectoris. It therefore seemed desirable to us to investigate the effect of epinephrine on patients with angina pectoris, for if all such patients should react to the drug by developing typical pain, it would follow that this knowledge might be applied for diagnostic purposes. It is not inferred that if this test is valid it need be tried in cases in which the diagnosis is certain, for then one would only be inducing an unnecessary attack of pain in a condition in which it is well known that any attack may have serious consequences. Numerous instances arise, however, in which the diagnosis of angina pectoris is by no means certain. This is particularly true when the symptomatology suggests the possibility of disease of the gallbladder, stomach or duodenum. Occasionally it is difficult to tell at the bedside whether pain or discomfort in the lower sternal region is due to upper abdominal or coronary artery disease. Here, certainly, it is important to decide whether the patient needs medical or surgical care.

Furthermore, there are instances in which it is certain that gallstones are present, and yet it is suspected that angina pectoris may also be

* Submitted for publication, June 20, 1929.

* Read by title at a meeting of the American Society for Clinical Investigation, Atlantic City, N. J., May 6, 1929.

* From the Medical Service of the Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

1. O'Hare, J. P.: Personal communication to the authors.

present. More definite proof that both conditions exist would naturally aid in deciding whether it was warranted to subject the patient to a major surgical operation.

METHOD

To determine the degree of regularity with which epinephrine produces typical attacks of pain in patients with angina pectoris, doses of 1 cc. of the drug were given subcutaneously to eleven such patients. For purposes of control similar doses of epinephrine were administered to ten young adults and to ten patients of the same age group as those with angina pectoris but without symptoms referable to the cardiovascular system. In each instance the subject was placed at rest in the recumbent position for thirty minutes or longer before the observations were begun. The same position was maintained throughout the experiment. After the systolic blood pressure had reached a constant level as determined by four or five consecutive readings, a control electrocardiogram was taken. Then, after again recording the blood pressure, the epinephrine was injected. Determinations of the blood pressure were made at intervals of two or three minutes for the first hour of the experiment and at five minute intervals for the remainder. A detailed record was kept of all subjective and objective responses on the part of each patient, and electrocardiograms were taken at frequent intervals. In each instance the observations were continued until the blood pressure had returned to its resting systolic level. If, at this time, the electrocardiogram still showed changes from the control tracing, additional records were taken at intervals of several hours.

RESULTS

A summary of the results obtained is presented in tables 1, 2 and 3. In ten of the eleven patients with angina pectoris a typical attack of pain resulted from the administration of epinephrine. The average time required for the development of pain was twenty minutes, with extremes of three and thirty-three minutes. The pain in each instance appeared a few minutes before the maximum systolic blood pressure was attained and lasted from five to thirty-seven minutes, with the exception of one case in which it remained for one hundred and ten minutes. In seven patients there was characteristic radiation of the pain, while in two, who had had radiating pain in some spontaneous attacks, there was only localized pain during the experiment. In four cases the attack was brought to an end by nitroglycerin or amyl nitrite, while in one, because the nitrites gave only transient relief, one-quarter grain (0.016 Gm.) of morphine was administered hypodermically. The single patient who did not respond to the test became extremely upset when the purpose of the experiment was explained to him, and basal blood pressure readings were obtained only after more than an hour's rest. Then a few minutes after the injection of the drug he became excited, restless and very angry. As a result, the systolic blood pressure rose to over 200 mm.; but on reassuring the patient and removing the electrocardiograph electrodes, it quickly dropped to its resting level. No pain was experienced. It is felt that this experiment can

TABLE 1.—*Results in Patients with Angina Pectoris*

Name	Age	Diagnosis*	Duration of Angina Pectoris	Control Electrocardiogram	Resting Systolic Pressure	Maximum Systolic Pressure†	Maximum Pulse Pressure Increase†	Maximum Pulse Rate Increase†	Onset of Pain, Minutes After Injection	Location of Pain	Radiation of Pain	Duration of Pain, Minutes	Nitrites	Maximum Change in Amplitude of T-2, Mm.†
M. S.	52	Pulmonary emphysema; diabetes mellitus	3 yr.	Delayed A-V conduction	125	220	60	26	22	Retrosternal	To left arm	8	+	+1.3
S. G.	58	Chronic constipation	8 mo.	Sinus rhythm; left axis deviation; T-1, 2, 3 diphasic	135	210	63	41	28	First left interspace	To above left scapula	17	+	+5.0
I. S.	46	Parkinson's disease	4 yr.	Sinus rhythm; left axis deviation	125	210	65	50	3	Retrosternal	0	5	0	+3.8
H. N.	73	Carcinoma of ascending colon; secondary anemia	4 wk.	Sinus rhythm; left axis deviation; T-3 iso-electric	115	140	29	5	25	Retroxiphoid	0	20	0	+1.2
H. H.	65	Duodenal ulcer	7 mo.	Sinus rhythm; T-3 inverted	158	194	40	36	22	Retrosternal; upper part of back	To left axilla	26	+	+1.4
G. G.	56	Pulmonary emphysema	3 mo.	Sinus bradycardia; R-3 notched; T-3 inverted	116	162	37	35	28	Second right interspace	To interscapular region	20	0	+1.3
J. E.	50	Psoriasis	3 wk.	Sinus rhythm; "coving" lead I; T-1 inverted; T-2 and T-3 diphasic	130	142	6	21	7	Retrosternal	To jaws	10	+	+0.8
E. A.	50	Arteriosclerosis	4 yr.	Sinus rhythm; left axis deviation; T-1 diphasic; T-2 diphasic	148	185	40	27	33	Retrosternal	0	12	0	+1.4
M. B.	53	Adenoma of prostate	5 wk.	Sinus rhythm; left axis deviation; P-3 and T-3 inverted	122	190	54	46	8	Retrosternal	To left arm	37	0	+3.4
J. G.	55	Umbilical hernia	8 mo.	Sinus bradycardia; left axis deviation; T-3 inverted	90	190	60	38	25	Retrosternal	To jaws	110	+	+0.5
Average					126.4	184.3	45.4	32.5	20.1			27.1		+2.01

* In addition to angina pectoris.
† After the injection of epinephrine.

TABLE 2.—*Results in Elderly Patients Without Angina Pectoris*

Name	Age	Diagnosis	Control Electrocardiogram	Resting Systolic Pressure	Maximum Systolic Pressure*	Maximum Pulse Pressure Increase*	Maximum Pulse Rate Increase*	Maximum Change in Amplitude of T-2, Mm.*
I. L.	68	Carcinoma of cecum; secondary anemia	Sinus rhythm; few premature beats	130	176	44	46	+0.5
M. S.	42	Lobar pneumonia; syphilis of central nervous system	Sinus rhythm	130	175	47	15	+0.2
L. T.	61	Epidermophytosis	Sinus rhythm; left axis deviation; T-3 diphasic; intraventricular block	150	244	90	20	+3.9
H. G.	50	Multiple sclerosis	Sinus rhythm	120	154	36	18	−2.3
D. P.	51	Chronic lymphatic leukemia	Sinus rhythm; T-3 inverted; slurring R-2	100	134	34	21	−0.3
E. R.	43	Psychoneurosis	Sinus rhythm	122	130	16	11	−1.4
M. R.	62	Lobar pneumonia; convalescent	Sinus rhythm; left axis deviation	125	184	49	30	+1.4
R. R.	58	Dibothryocephalus latus infestation	Sinus rhythm	133	138	5	27	−1.9
S. R.	63	Carcinoma of stomach; secondary anemia	Sinus rhythm	120	156	38	21	−0.8
M. F.	55	Secondary anemia	Sinus rhythm; T-3 inverted	120	144	22	20	−0.7
Average				125.0	163.5	38.1	22.9	−0.04

* After the injection of epinephrine.

TABLE 3.—*Results in Young Adults*

Name	Age	Control Electrocardiogram	Resting Systolic Pressure	Maximum Systolic Pressure*	Maximum Pulse Pressure Increase*	Maximum Pulse Rate Increase*	Maximum Change in Amplitude T-2, Mm.*
B. J.	23	Sinus rhythm	114	146	38	12	−1.2
E. K.	21	Sinus rhythm	120	169	47	18	−1.8
F. K.	24	Sinus rhythm	116	144	27	25	+0.6
A. M.	30	Sinus rhythm	104	132	18	52	+1.5
C. E.	27	Sinus rhythm; diphasic T-3	122	138	24	16	+0.2
S. H.	22	Sinus rhythm	108	174	54	37	+1.1
D. S.	38	Sinus rhythm	98	130	36	34	+0.4
J. R.	23	Sinus rhythm	116	146	20	14	−3.0
A. E.	27	Sinus rhythm; ventricular premature beats; P-3 diphasic	120	170	53	27	−2.5
A. R.	26	Sinus rhythm	120	136	16	22	−3.3
Average			113.8	148.5	33.3	24.7	−0.8

* After the injection of epinephrine.

hardly be used in evaluating the results of the investigation. Four of the patients who developed anginal pain with 1 cc. of epinephrine had been given 0.5 cc. on a previous occasion without such effect.

None of the elderly control subjects or young adults experienced anginal pain. One of the former group, however, did report a sensation of dull oppression behind the xiphoid three minutes after the injection. This lasted for six minutes and disappeared before the systolic pressure had reached its peak. In addition, one patient from each of the two control groups reported momentary sticking, precordial pain at the height of epinephrine effect.

Blood Pressure.—In the ten patients with angina pectoris who reacted to the test with an attack of typical pain, there was an average rise in systolic blood pressure of 58 mm. of mercury, with limits of 12 and 100 mm. In six patients the rise amounted to more than 65 mm. The systolic pressure in the group of elderly controls showed an average rise of 39 mm. of mercury, with limits of 5 and 94 mm. In seven patients the rise was over 33 mm. There was an average rise of systolic pressure in the group of young adults of 33 mm., with extremes of 16 and 66 mm. Six patients had an increase of 30 mm. or more. The average time required for the attainment of the maximum systolic pressure was between twenty and twenty-four minutes in all three groups of cases. In the ten patients with angina pectoris there was an average increase in pulse pressure of 45 mm. of mercury. In the elderly controls there was an average increase of 38 mm., and in the young adults the average was 33 mm. of mercury. In general, therefore, it may be said that the rise in systolic blood pressure and pulse pressure was somewhat greater in the patients with angina pectoris than in the other two groups.

Pulse Rate.—The average pulse rate increase in the ten patients with angina pectoris was 33 beats per minute. For the elderly controls the average increase was 23 beats per minute, and for the young adults it was 25 beats per minute. Here again the effect, in general, was greater in the patients with angina pectoris than in the others.

Symptoms and Signs.—Practically every patient showed symptoms and signs characteristic of the effect of epinephrine. These included tremor, palpitation, sweating, pallor, flushing, nervousness, weakness and pulsations in the neck and epigastrium. Usually these symptoms and signs were of only moderate severity, and none of the patients with angina pectoris displayed the marked reactions which occur in persons sensitive to epinephrine.

Electrocardiographic Changes.—The literature contains few reports of electrocardiographic observations during attacks of angina pectoris.

Bousfield [2] obtained a record on a patient with aortic insufficiency during a spontaneous attack which showed block of the right branch of the bundle of His. The curve taken after the pain had subsided showed only upwardly convex S-T intervals and sharply inverted T waves in leads II and III with no conduction defect. Feil and Siegel [3] obtained records during the attack in four patients, the pain being produced by mild exercise in three instances and occurring spontaneously in one. Three of these showed inversion of the S-T interval in leads I and II during the pain. One showed increased amplitude of the T wave in lead II. With the cessation of pain, the record in each instance returned to normal. One patient showed no electrocardiographic changes during the attack.

A detailed study was made of all electrocardiograms of each patient in the present investigation. In none of the groups were there appreciable or constant changes in the P wave amplitude, P-R interval, QRS complex, Q-T duration or in the contour of the S-T interval. In a few patients a preexistent sinus arrhythmia was accentuated, and in others sinus arrhythmia was initiated by the drug. Ectopic beats of nodal, auricular and ventricular origin were produced with equal incidence in all three groups of cases, beats of ventricular origin being the most commonly observed in each group. One patient with angina pectoris who had a normal control electrocardiogram showed nodal rhythm in two records taken at the height of the epinephrine effect. One patient with a P-R interval of three-tenths seconds in the control tracing developed ventricular tachycardia at the onset of anginal pain (fig. 1). Nitroglycerin was given immediately, and a curve taken two minutes later showed a return to the delayed A-V conduction of the control record. In the other patients no abnormalities of rhythm, except ectopic beats, were observed.

Particular attention was paid to the amplitude of the T wave in all records because this wave is clinically important from the point of view of disease of the coronary artery. Each patient with angina pectoris showed an increase in the amplitude of the T wave in lead II after the injection of epinephrine. The average increase observed was 2 mm., with extremes of 0.5 and 5 mm. Figure 2 shows the type of response of this group. The T wave in lead II showed a diminution of amplitude in six of the elderly controls and an increase in the other four, the average for the entire group being a diminution of 0.04 mm. with extremes of minus 1.9 and plus 3.9 mm. In the young adults (fig. 3),

2. Bousfield, G.: Angina Pectoris: Changes in Electrocardiogram During Paroxysm, Lancet **2**:457 (Oct. 5) 1918.

3. Feil, H., and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, Am. J. M. Sc. **175**:255 (Feb.) 1928.

there was an average fall in T wave amplitude in lead II of 0.8 mm., five cases showing an increase of from 0.4 to 1.5 mm. and five a decrease of from 1.5 to 3.3 mm. In each group the maximum change in the T wave was observed at the time of the maximum systolic blood pressure reading, and in each the average time required for the wave to return to its normal amplitude was a little less than two hours. The alterations in the T wave in leads I and III were not significantly different from those in lead II. The changes observed in the curves of the two control groups agree in general with those recorded by Clough [4]

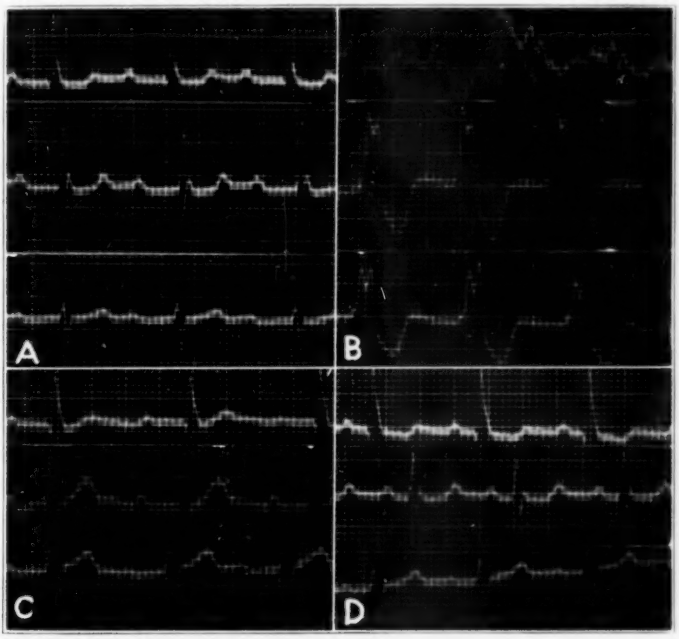

Fig. 1.—Electrocardiograms of patient, M. S., with angina pectoris. The customary three leads are shown in all figures with one-fifth and one-twenty-fifth seconds indicated. *A*, control record showing delayed A-V conduction; *B*, record at onset of pain, showing ventricular tachycardia; *C*, record two minutes after *B*, pain subsiding, showing return to delayed A-V conduction with T waves of increased amplitude; *D*, record seventeen minutes after *C*, showing return of T waves to original amplitude.

in normal soldiers and in soldiers with "irritable heart" after doses of 0.5 cc. of epinephrine.

4. Clough, H. D.: Studies on Epinephrin: III. Effect of Epinephrin on the Electrocardiograms of Patients with "Irritable Heart," Arch. Int. Med. **24**:284 (Sept.) 1919.

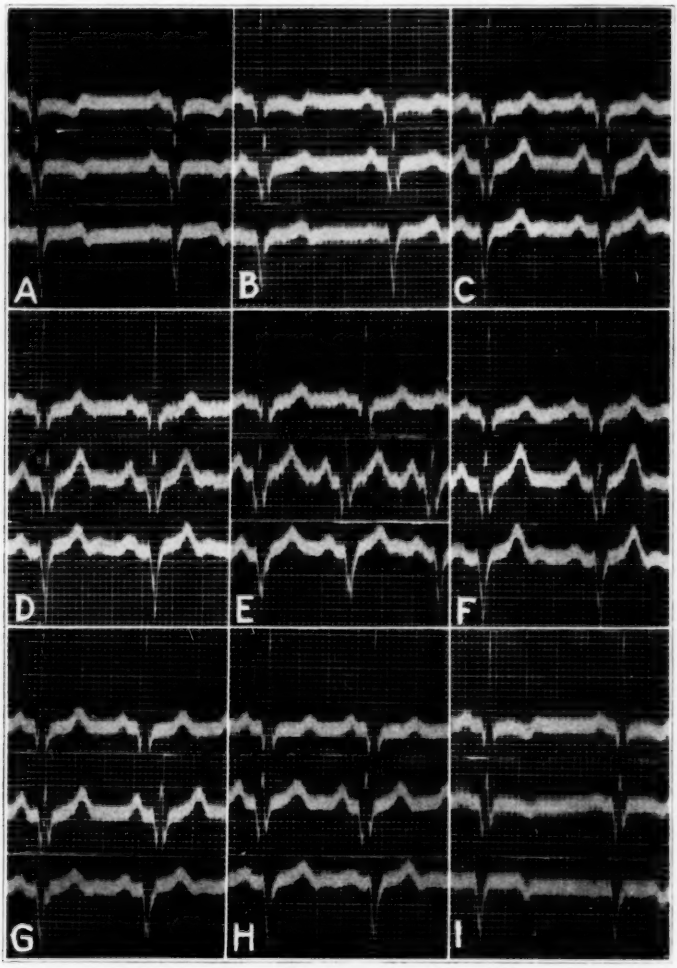

Fig. 2.—Electrocardiograms of patient, S. G., with angina pectoris, showing progressive increase in amplitude of T waves after the injection of epinephrine, with subsequent return to normal. *A*, control record, blood pressure 135 systolic and 72 diastolic; *B*, fifteen minutes after injection of epinephrine, blood pressure 142 systolic and 68 diastolic; *C*, twenty-one minutes after injection of epinephrine, blood pressure 178 systolic and 68 diastolic; *D*, twenty-eight minutes after administration of epinephrine, at onset of anginal pain, blood pressure 200 systolic and 80 diastolic; *E*, three minutes after *D*, blood pressure 210 systolic and 84 diastolic, pain severe; nitroglycerin $\frac{1}{100}$ grain (0.00065 Gm.) administered at end of this record; *F*, four minutes after *E*, blood pressure 190 systolic and 78 diastolic, pain diminishing; *G*, ten minutes later, at end of pain, blood pressure 144 systolic and 70 diastolic; *H* and *I*, at thirty minute intervals after *G*, showing return to original T wave amplitudes as the blood pressure dropped to 122 systolic and 68 diastolic.

COMMENT

The pathogenesis of angina pectoris is still obscure. The theory of Keefer and Resnik,[5] however, that anginal pain arises as the result of anoxemia of a restricted part of the myocardium seems the most satisfactory of the many explanations offered to date. Epinephrine increases the amount of work which the heart is called on to perform as a result of the elevation of blood pressure and the increase in metabolism. It also increases the coronary blood flow. The former effect probably is more marked than the latter. In normal patients the increased oxygen

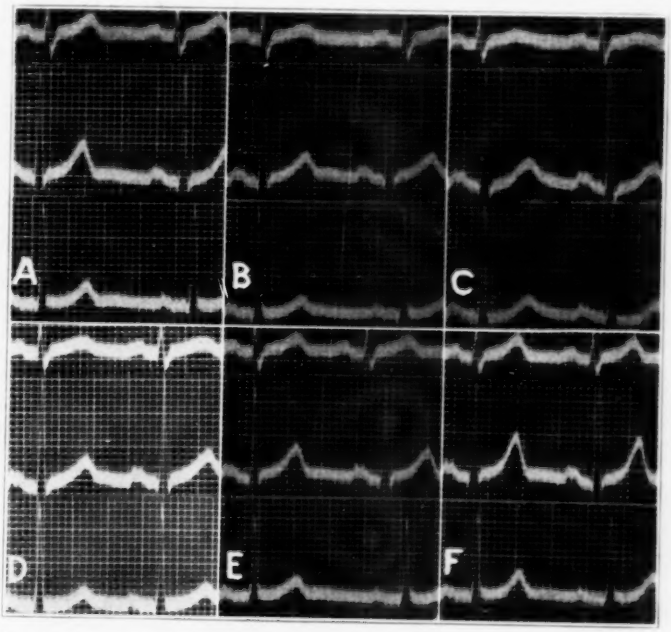

Fig. 3.—Electrocardiograms of young adult subject, B. J., showing slight decrease in amplitude of T waves with subsequent return to normal. *A*, control tracing, blood pressure 114 systolic and 66 diastolic; *C*, record at height of epinephrine effect, twenty-seven minutes after injection, blood pressure 146 systolic and 60 diastolic; *D*, one hour after *C*, blood pressure 122 systolic and 66 diastolic; *E*, one hour after *D*, blood pressure 116 systolic and 70 diastolic; *F*, one hour after *E*, blood pressure 114 systolic and 70 diastolic.

requirement of the myocardium after the administration of epinephrine may or may not be compensated for completely by increased coronary

5. Keefer, C. S., and Resnik, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, Arch. Int. Med. **41**:769 (June) 1928.

blood flow. When, for any reason, the coronary blood flow is already below normal, it is logical to suppose that following injections of epinephrine a definite disproportion between the increased work of the heart and the available supply of oxygen will develop. If this is true, the occurrence of localized anoxemia of the myocardium after the injection of epinephrine into patients predisposed to such an occurrence by coronary artery disease (the probable underlying pathology in all our patients with angina pectoris) or by aortic regurgitation is easily understood. Assuming, therefore, that anginal pain is due to localized anoxemia of the myocardium, a rational explanation of the results obtained in the present study is available.

Anginal attacks are, of course, never without danger. Because epinephrine has now been shown to produce typical pain with great regularity in patients with angina pectoris, therapeutic use of the drug in such patients should be carried out with great caution. This may apply likewise to the use of ephedrine. When the diagnosis of angina pectoris is certain, there is no indication for the use of epinephrine as a diagnostic measure. Occasionally, however, patients are seen in whom, as pointed out previously, the diagnosis is doubtful; in such cases information as to the presence or absence of angina may be of the utmost importance.

CONCLUSIONS

1. Epinephrine was administered subcutaneously in doses of 1 cc. to three groups of persons: one group of eleven with angina pectoris, a second of ten of the same average age but without angina, and a third of ten normal young adults. In all but one patient with angina pectoris, typical pain resulted from the injection. In none of the control patients did this pain occur.

2. Electrocardiographic studies showed that following the injection of epinephrine the T wave in the anginal group increased slightly in amplitude, while in the other two groups it showed a tendency to decrease.

3. The increase in blood pressure and pulse rate was somewhat greater in the anginal group than in the others.

4. It is suggested that the production of anginal pain by the injection of epinephrine may serve as a diagnostic test for angina pectoris. The test would not be applicable when the diagnosis is certain but rather in doubtful cases or when there are other possible explanations for the symptoms, such as gallstones or disease of the stomach or the duodenum.

5. Because epinephrine produces typical pain with great regularity in patients with angina pectoris, therapeutic use of the drug in such patients should be carried out with great caution.

THE CAPILLARY CIRCULATION IN THE ALVEOLUS PULMONALIS OF THE LIVING DOG*

D. M. OLKON, M.D.
AND
MINAS JOANNIDES, M.D.
CHICAGO

In a previous paper [1] reporting the results of a capillaroscopic study of the pulmonary alveolus in the living dog, the capillary blood supply was merely mentioned. In this subsequent report, it is our purpose to describe the capillary circulation in detail.

METHODS AND RESULTS

It was stated in the previous report that the normal pleura may be regarded as a glass window through which one can study the structure and activity of the alveolus and its capillaries without disturbing the normal activity of these tissues.

Our observations were made by means of a Zeiss capillary microscope which was devised by Otfried Muller.[2] This microscope has a magnification of 60 and has a 6 volt lamp inside the tube of the microscope. The advantage of this instrument over others is that the light is direct and as the focus is moved the light moves with it so that the degree of illumination does not vary. Only a small amount of heat is given off by this lamp, so that no appreciable vasodilatation is noticed. Cedar oil or glycerin was spread over the field of observation, which gave a clearer vision.

Healthy dogs were used. The animal, which was quieted with scopolamine hydrobromide and ether analgesia, was studied with reference to its normal respiration, pulse and the skin capillaries. The lung was exposed by means of a thoracotomy incision, and the capillaries of the pleura and the lung were carefully observed before any changes were instituted. Two types of capillaries were seen, namely, the multicellular and the single cell. The term multicellular capillary is used for one in which the lumen is wide enough to permit more than one row of erythrocytes to pass through at the same time. A single cell capillary

* Submitted for publication, June 29, 1929.

* From the Departments of Neurology and Surgery, University of Illinois College of Medicine.

1. Olkon, D. M., and Joannides, Minas: The Structure of the Alveolus Pulmonalis of the Living Dog, to be published.

2. Muller, Otfried: Die Kapillaren der Menschlichen Korperoberfliche in gesunden und Kranken Tagen, Stuttgart, Ferdinand Enke, 1922.

is one in which the lumen is wide enough to permit only one row of erythrocytes to pass in a single file.

Surrounding the alveolus there is a multicellular capillary (figs. 1 and 2). This gives off one cell capillaries at given distances. These smaller capillaries are usually arranged at right angles to the multicellular capillary but may sprout out at any angle. Depending on the degree of contraction or expansion of the air units, one can see a variable number of single cell capillaries. When the alveolus is expanded, a smaller number of single-celled capillaries is seen. On the other hand, when

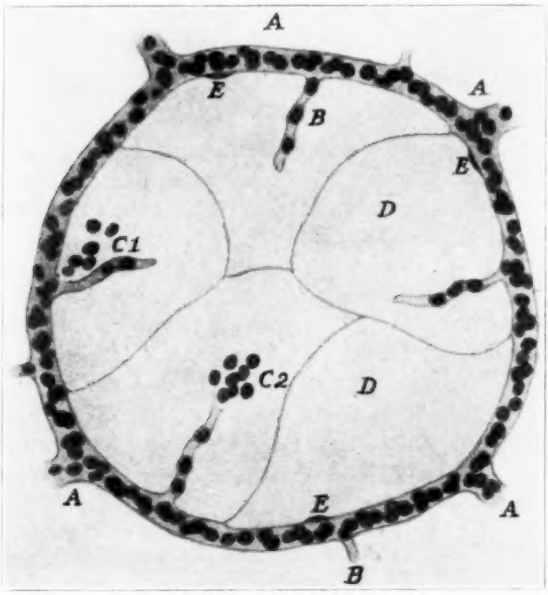

Fig. 1.—Diagram of alveolus and air units, showing capillaries in various states. *A* indicates a large multicelled capillary; *B*, a single cell capillary; C_1, a capillary rupture at the point of origin with liberated erythrocytes near the point of rupture; C_2, a single cell capillary ruptured at its distal end with liberated erythrocytes at that point; *D*, air spaces, and *E*, endothelial nuclei of the multicellular capillary.

the alveolus is contracted, a larger number of these capillaries can be seen.

When the intrapulmonic air pressure is increased so that the lung becomes distended up to a volume greater than the chest cavity, the single cell capillaries become thinned out and only a small number remain visible. As the distention of the lung is decreased, these capillaries again gradually become visible.

The flow of blood through the capillaries was greatly increased when the lung was distended to a volume greater than normal. Coincidentally, the one cell capillaries assumed a straighter outline and a deeper color. Likewise when the pressure was suddenly reduced, the flow in the larger capillaries assumed a to-and-fro movement, stopping for a moment and then moving again.

When the alveolus was overdistended with air, the capillaries showed changes in pattern in that they expanded and assumed a fusiform shape. These returned to their original tubular form when the alveolus contracted back to the usual size. Morover, at the distal end of the single cell capillaries and also at the point of origin, free floating erythrocytes were seen, indicating that some of these small capillaries ruptured at these points because of the increased alveolar distention. In some of the single cell capillaries, a contraction was noticed in the middle half. This

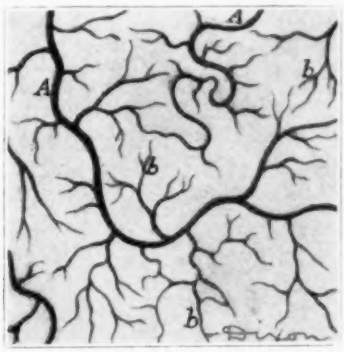

Fig. 2.—Diagram of capillary bed in the pia-arachnoid, showing normal arrangement of the capillaries. *A* indicates a normal large capillary of the pia-arachnoid in the living dog, and *b*, single cell capillaries given off principally at right angles.

contraction left a few erythrocytes immobilized close to the point where the capillary dips into the alveolus, assuming the picture of stasis (fig. 3).

Although these changes in the capillaries appear to be intimately associated with changes in the size of the alveolus, we believe that the capillaries per se may act independently of alveolar changes. In a study of the cerebral capillaries it was found that when the dog received a sufficient dose of strychnine to induce convulsions, the single cell capillaries seemed first to contract as the rigor appeared. During the convulsion they were almost obliterated from view (fig. 3). When the convulsions stopped, there was a state of intermittent contraction and dilation of the capillaries, and at this time hemorrhages appeared at points similar to those of the capillaries in and about the alveolus (fig. 1). In view of the fact that the cerebrum was exposed and there

was no increase of intracranial pressure because the dura was incised, it is safe to assume that these changes in the capillaries have occurred by changes in their tonus (fig. 3 *c*). Further evidence as to the presence of a tonus in even the smallest capillaries has been the effect of increased muscular activity on the alveolar capillaries. The changes in the alveolar capillaries that were noticed by hyperventilation of the lungs were also noticed when rigor was substituted. The activity of the capillaries in the lung is similar to that of capillaries elsewhere in the body. When changes occurred in the capillaries of the skin and the brain, under given conditions, similar changes were also noticed in the alveolar capillaries. Thus during the stage of excitement when the animal struggled the

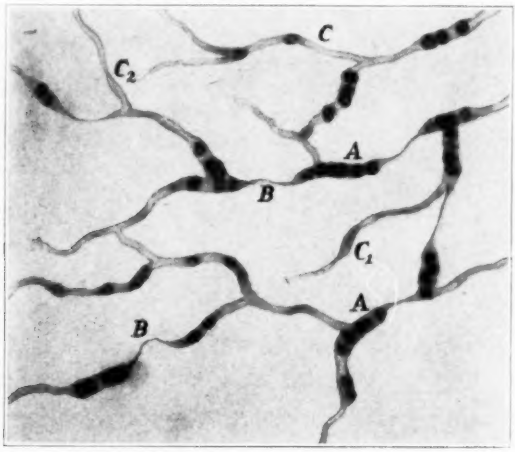

Fig. 3.—Diagram of capillary bed of the pia-arachnoid, showing changes similar to those of the lung capillaries. *A* indicates a portion of the capillary in which the erythrocytes are immobilized following spasm in a single cell capillary; *B*, a portion of the capillary showing spastic contraction; *C*, a portion of the capillary showing atony after contraction; C_1, a dilated portion of the capillary following spasm, empty of erythrocytes; C_2, a partial contraction of the capillary, empty of erythrocytes. *C*, C_1 and C_2 show the slowness of the capillary recovery to their physiologic norm after injury (time: from two to five minutes). (Primary hemorrhages almost always take place in these smallest units of the vascular tree and not formerly described in fixed tissue studies.)

superficial capillaries showed massive hemorrhages. Similar hemorrhages were also noticed in the capillaries of the lungs, liver, kidney, bladder and intestine. It would seem, therefore, that a study of the superficial capillaries is a good index of activity in the capillaries of other organs such as the brain, stomach, intestine, lungs, kidneys and bladder.

CONCLUSIONS

1. The capillary blood supply of the alveolus pulmonalis appears to be unique, and there seems to be an intimate relation between the changes of air migration in the alveolus and its capillary blood supply.

2. The finding of capillary changes in and about the alveolus suggests a probable index to changes which are at times symptomatic without gross clinical observations in the lungs.

3. The outstanding capillary changes observed were: contraction of the capillaries, rupture of the right angle single cell capillaries and microscopic hemorrhages in the immediate vicinity.

4. Mild trauma, such as hyperventilation or increased muscular contraction, gives rise to capillary hemorrhages heretofore not described in the histologic studies of fixed tissues.

5. The study of the superficial capillaries may be considered a good index of the earliest visible changes occurring in the capillary blood supply in organs of living animals under increased activity.

310 South Michigan Avenue.

3750 Broadway.

HEAT AND EFFORT SENSITIVENESS COLD SENSITIVENESS

RELATIONSHIP TO HEAT PROSTRATION, EFFORT SYNDROME, ASTHMA, URTICARIA, DERMATOSES, NONINFECTIOUS CORYZA AND INFECTIONS *

W. W. DUKE, M.D.
KANSAS CITY, MO.

In this paper I shall enumerate a series of relatively common illnesses, many of them serious, which are caused, rather frequently, I believe, by a disorder in the heat regulating mechanism. The illnesses include heat prostration, symptoms of effort syndrome, noninfectious coryza, asthma, urticaria, dermatoses and other miscellaneous ailments to be mentioned. They are commonly diagnosed neurasthenia, psychasthenia, allergy, atopy, vagotonia and eczema. The patients are hypersusceptible to infection during their reaction to heat or cold, especially infection in the nasorespiratory tract, and for this reason, their disorders are often classed with the infections.

HEAT REGULATING MECHANISM

Whatever the heat regulating mechanism may be, and wherever it may be, certain it is that it is an important and effective mechanism. It is important because it makes the difference between warm-blooded and cold-blooded animals. It is effective because it maintains body temperature at a relatively constant level in the normal person whether he resides at the equator or in the polar regions and whether he generates an enormous amount of heat through effort, or whether he is at rest or asleep.

Investigation of the heat regulating mechanism has interested many eminent physiologists, including Claude Bernard, Richet,[1] Cannon [2] and others. Many interesting facts of fundamental importance have been disclosed which should interest pathologists and physicians, especially those whose work brings them in contact with disorders commonly classified as allergy or atophy, and with the so-called neuroses and the dermatoses.

Body temperature is kept normal and constant through the automatic control of heat generation and of heat loss. The automatic con-

* Submitted for publication, Sept. 4, 1929.

* Read before the Association for Research in Nervous and Mental Diseases, Dec. 28, 1928.

1. Richet, C.: Chaleur dictionaire de physiologie, 1898, vol. 3, p. 178.

2. Cannon, W. B., et al.: Am. J. Physiol. **61**:528, 1927.

trol is grossly strengthened by voluntary actions of a person when he feels too hot or too cold. Whereas the automatic and voluntary control of heat generation is grossly important, it is not so effective, I believe, under average conditions as the automatic control of heat loss. Both mechanisms, however, are important.

Overheating.—Heat generation is increased in a given organ by increase in its activity, whether the organ is the brain, a gland or a muscle. If excess heat thus generated is not adequately removed by increased blood flow, the organ is likely to become overheated and is likely to behave badly. An organ may be permanently damaged by overheating. The temperature at which an organ works to its best advantage is unfortunately dangerously near a temperature that is damaging to its function, so that prompt removal of heat from an active organ ranks in importance, I believe, with the prompt removal of waste products. Hyperemia is looked on as useful for carrying additional food and oxygen to an organ during periods of activity, and for the removal of carbon dioxide and other waste products. The probability is that it is equally useful for the prompt carrying away of heat. In fact, it might be well to call heat a waste product in the same sense that Mendel in his lectures to students of physiology, calls heat a waste product.

These facts seem so obvious that they should hardly need discussion. However, it may be well to emphasize the gross importance of a slight excess of heat as a disturbing and dangerous element by quoting several interesting experiments. Moore and Oslund [3] stated that the temperature of the scrotum is several degrees below the average temperature in the peritoneal cavity. By wrapping ram's scrotum in such a way as to cause a rise in scrotal temperature toward the temperature of the peritoneal cavity, the spermatozoa were made to disappear from the testicle almost completely within a few months. These observers believed that this phenomenon was due actually to a rise in temperature above the optimum for this tissue, and that the absence of spermatozoa in undescended testicles is due primarily to the fact that peritoneal temperature is above the optimum for the normal life of spermatozoa. Heymans [4] stated that the brain is more sensitive to high temperature than other organs and that a brain temperature of from 42 to 43 C. is fatal for rabbits. Heymans and Heymans [5] found that brain temperature exceeding from 45 to 46 C. in dogs caused death of the brain cells.

3. Moore, C. R., and Oslund, R.: Am. J. Physiol. **67**:575, 1924.

4. Heymans, J. F.: Arch. internat. d. Pharmakol. e. d. Therap. **25**:1, 1919.

5. Heymans, J. F., and Heymans, C.: Ann. Soc. sc. de Bruxelles **46**:294, 1926.

Storm van Leeuwen and van der Mode [6] found that reflexes in the cat were most active at a temperature of 38 C., and were rendered less active by a rise in temperature above this point. Lowering of temperature to 35 C. had little effect on reflexes, but lowering below this point reduced them. All observers seemed to find that animals stood a lowering of temperature much better than a rise above the optimum.

The foregoing statements refer to overheating of individual organs. Activity of several organs gives rise to a general increase in body temperature under normal conditions, unless heat loss from the nose, bronchial tubes or skin can be adequately increased. Heat loss can be increased through dilatation of blood vessels leading to the three important cooling surfaces, the skin, the mucous membrane of the bronchial tree and the mucous membrane of the nose. Cooling is aided by the secretion of moisture and evaporation from these surfaces, and by an increase in the depth and rapidity of respiration. If air is dry, evaporation is an important factor in the process of cooling. If air is saturated with moisture, the surfaces are cooled only by convection and conduction to the outside air. If outside air is moist, but cool, it may adequately cool the body. If, however, the outside air is moist and warm, heat loss is seriously retarded, and under these conditions, it is extremely easly for activity to cause overheating, illness and death.

Cerebral Heat Control.—Automatic control of body temperature is accomplished through the coordinated action of many structures that try to govern heat production and heat loss. Body temperature is regulated partly by a thermostat-like mechanism in the region of the thalamus. Barbour,[7] Moore,[8] Hashimoto [9] and others demonstrated that by cooling an area in the region of the corpus striatum, rectal temperature can be increased, whereas by warming this same area, rectal temperature can be reduced. Isenschmid and Krehl [10] demonstrated that the power to resist external changes in temperature without variation in body temperature is lost in animals if the midbrain is sectioned just anterior to the center of the optic thalamus. Experimental injury to the optic thalamus in pigeons caused them to lose their power

6. Storm van Leeuwen, W., and Van der Mode, M.: Arch. f. d. ges. Physiol. **165**:37, 1916.

7. Barbour, H. G.: Physiol. Rev. **1**:295, 1918; Arch. f. exper. Path. u. Pharmakol. **70**:1, 1912; J. Pharmakol. & Exper. Therap. **14**:65, 1919; Antipyretics: III. Acetylsalicylic Acid and Heat Regulation in Fever Cases, Arch. Int. Med. **24**:624 (Dec.) 1919; Am. J. Physiol. **55**:295, 1921; ibid. **67**:366, 1924.

8. Moore, L. M.: Am. J. Physiol. **46**:244, 1918; ibid. **1**:102, 1919.

9. Hashimoto, M.: Arch. f. exper. Path. u. Pharmakol. **68**:370, 1915.

10. Isenschmid, R., and Krehl, L.: Arch. f. exper. Path. u. Pharmakol. **70**:1 and 109, 1912.

to resist changes in external temperature (Rogers).[11] Resection of the stellate ganglion had the same effect (Freund).[12] Such experiments harmonize well with clinical knowledge. Diseases of the brain caused by hemorrhage, tumor, meningitis or trauma are likely to be associated with rapid oscillations in body temperature. There should be little doubt concerning the existence of automatic control of temperature by brain centers.

Endocrine Heat Control.—Several of the glands of internal secretion, especially the suprarenal, thyroid and pituitary glands, play rôles in the control of temperature. The effect of hyperthyroidism and hypothyroidism on the metabolic rate is so well known as to need no discussion. When the metabolic rate is abnormal in a case of dysthyroidism, the altered rate of heat production is often compensated for by an altered rate of heat loss, so that body temperature is not correspondingly altered. The suprarenal gland has an effect both on the rate of heat production and on that of heat loss, the former through modifying the metabolic rate, the latter through an effect on vascular tone and therefore on blood flow to cooling surfaces. Boothby and Sandiford[13] reviewed the literature on the subject of the suprarenal gland in relationship to heat production, and confirmed the results of other observers in showing that the injection of epinephrine hydrochloride into animals even in physiologic doses noticeably increases the rate of heat production. Aub, Forman and Bright[14] found that removal of the suprarenal glands was followed by a drop of about 25 per cent in the metabolic rate, even though the temperature of the body remained the same. McIver and Bright[15] found that direct or reflex stimulation of suprarenal secretion promptly augments metabolism, often as much as 50 per cent. Cannon, Querido, Britton and Bright[16] found evidence of an effect of suprarenal secretion on the heart rate in animals exposed to a cold environment or following the introduction of cold water into the stomach. This cold reaction could be stopped by application of heat. In animals in which one of the suprarenal glands was denervated, and the other removed, the heart rate was not effected by cold. Furthermore, they demonstrated an increase in metabolic rate in normal sub-

11. Rogers, F. T.: Relation of Cerebral Hemispheres to Arterial Blood Pressure and Body Temperature Regulation; Preliminary Note, Arch. Neurol. & Psychiat. **4**:148 (Aug.) 1920; Am. J. Physiol. **49**:271, 1919.

12. Freund, H.: Arch. f. exper. Path. u. Pharmakol. **46**:236, 1911; ibid. **72**: 295, 1913; Handb. d. norm. u. path. Physiol. **17**:86, 1926.

13. Boothby, W. M., and Sandiford, I.: Am. J. Physiol. **66**:93, 1923.

14. Aub, J. C.; Forman, J., and Bright, E. M.: Am. J. Physiol. **55**:293, 1921; **61**:326, 1922.

15. McIver, M. A., and Bright, E. M.: Am. J. Physiol. **68**:622, 1924.

16. Cannon, W. B.; Querido, A.; Britton, S. W., and Bright, E. M.: Am. J. Physiol. **79**:1, 1927.

jects after the introduction of cold water into the stomach through a tube. If cold applications were gross enough to cause shivering, the rise in metabolic rate frequently amounted to as much as 50 to 90 per cent above the basal rate. They concluded that the same conditions that increase the suprarenal secretion in animals increase the metabolic rate in man, and that "a disturbing heat loss evokes activity of the adrenal medulla and that the output of adrenin by hastening combustion, serves to protect the organism against cold." They supported the contention of Voight and Ruebner that there exists in the body a mechanism for the chemical augmentation of metabolism. They believed that the secretion of the suprarenal gland is augmented by cold, and that this serves to increase the rate of heat production. Suprarenal secretion is believed to be governed both by the temperature of the blood and by sensory nerve impulses coming from the skin and other areas caused by heat or cold.

The pituitary hormones have a profound influence on growth and metabolism, but apparently little effect on heat production. This has been intensively studied clinically and experimentally, and negative or variable results have been obtained. Both suprarenal hormones and pituitary hormones, however, are interesting in relationship to heat loss, since the hormones of either gland have a profound influence on vascular tone. The intracutaneous injection of an extract of the suprarenal or pituitary gland in dilute solution causes vasoconstriction and capillary constriction with blanching of the tissues. There is some uncertainty as to whether or not there is an adequate quantity of epinephrine in normal blood to effect vascular tone. Krogh [17] was inclined to believe that pituitary hormone is more important than epinephrine in this rôle—that is, as a normal regulator of capillary tone. Rehberg and Carrier [18] found that extirpation of the pituitary gland caused loss of capillary tone in frogs, and Pohle [19] found that its extirpation can lead to actual edema.

Histamine Effects.—The intracutaneous injection of a dilute solution of histamine causes local hyperemia, itching and edema—in fact, typical hives (Eustis [20] and others). Lewis [21] recently emphasized the importance of histamine and allied bodies (which he called H-bodies) in relationship to vascular tone under physiologic conditions. His work

17. Krogh, A.: Internat. Ztschr. f. phys. chem. Biol. **1**:491, 1914; J. Physiol. **53**:399, 1919.

18. Rehberg, P. B., and Carrier, E. B.: Skandin. Arch. f. Physiol. **42**:250, 1922.

19. Pohle, E.: Arch. f. d. ges. Physiol. **182**:215, 1920.

20. Eustis, A.: New Orleans M. & S. J., April, 1914, vol. 66.

21. Lewis, T.: Heart **11**:151, 1924; Blood Vessels of Human Skin and Their Responses, London, Shaw & Sons, 1927.

is based on a study of the blood vessels of the skin, but he inferred that the same influence may be exerted on other blood vessels, for example, those supplying muscle tissues. Histamine-like bodies are interesting in that they are liberated by putrefaction from protein foods and also by normal catabolic processes, and have been isolated from normal tissues. On injection histamine has an effect opposite to that of pituitary or epinephrine extract in that it causes capillary dilatation almost immediately. Lewis found that histamine has a more profound effect on capillary tone than pituitary or suprarenal extract because vessels that are dilated with histamine cannot be contracted with either pituitary or suprarenal extract even when used in relatively concentrated solution.

Pituitary hormone, suprarenal hormone and histamine-like bodies, therefore, working antagonistically and causing, respectively, vasoconstriction and vasodilation, must be looked on as possibly important factors in the regulation of blood supply and therefore important factors in the regulation of heat loss. As histamine-like bodies are liberated by normal metabolic processes, their influence in causing vasodilation and increased removal of heat cannot be overlooked as probably important factors in the regulation of the temperature both of active organs and of the body as a whole. This phase of the subject will be referred to subsequently in a clinical discussion.

Sensory Heat Control.—Whereas, in the previous paragraphs, emphasis has been laid on hidden mechanisms that effect heat production and heat loss, I would not lead the reader to infer that the more obvious factors are less important. For example, the sense organs for the perception of heat and cold have, no doubt, a rapid effect on both heat generation and heat loss, both automatic and voluntary. Richet[3] believed that reflexes from sensory nerves may cause the initial response to change of temperature. He noticed polypnea immediately after exposure of dogs to sunlight, even at a time when rectal temperature was temporarily falling. The fact is, that the application of heat to the skin in doses that could hardly cause any marked change in blood temperature may cause a quick change in the metabolic rate. Furthermore, the immediate effect of exercise on the respiratory rate is so obvious and gross as not to need experimental proof. It would be interesting to note whether or not there is a reduction in the tone of the muscles of the bronchioles and pulmonary vessels coincident with exercise which would aid in body cooling. This, one would think, should occur, but so far as I know, has not been experimentally proved.

Surface Temperature in Relation to Rectal Temperature.—Contrary to general belief, temperature is not the same in different parts of the body, nor is it constant in all localities under varying conditions of external temperature. For example, the temperature of the skin and

that of tissues immediately beneath the skin are grossly below rectal temperature. The average temperature of the skin, depending on the body covering, may vary from 24 to 34 C., and after exposure to cold, may fall grossly below this. The temperature of the skin and that of the muscles of the extremities are, as a rule, much below rectal temperature, and on exposure to cold, are reduced rapidly and to a surprising degree below rectal temperature. The temperature of the skin under the influence of exercise was studied by Benedict and Parmenter,[22] who found that the average temperature of the skin is not increased, but is actually reduced one or more degrees by physical exercise in cold air, even though the metabolic rate may be increased as much as 500 per cent.

Whereas, under basal conditions about 75 per cent of body heat is lost by radiation from the skin, this is evidently not the case during periods of gross activity, when a large proportion of the excess heat must be lost by evaporation and convection from the respiratory tract. Apparently, constriction of surface blood vessels forces blood into internal channels during exercise, where it is used in supplying active tissues. It discharges the excess heat thus collected, through the pulmonary circulation into the respiratory tract. Whereas the respiratory tract may be a minor factor in body cooling during periods of rest, it becomes a gross factor during periods of high grade activity. The respiratory tract is a greater factor in heat removal in animals that do not sweat, such as dogs, than it is in man.

THEORY OF TEMPERATURE CONTROL

Richet's theory of the normal control of body temperature assumes that reflexes caused by the sensation of heat or cold on surface tissues give rise to prompt reactions that control body temperature under the usual conditions of living—that is, they modify heat production and heat loss so that body temperature remains the same. He believed that mechanisms affected by the temperature of the blood itself are less important, and play important parts only after considerable change in the temperature of the blood has occurred.

Bazett [23] combined the views of Richet, Meyer's theory of a dual heat center and the experimental work of Sherrington, and suggested the following hypothesis. The control of body temperature is almost entirely reflex, caused by sensory impulses from surfaces, caused by heat or cold. He believed that changes in blood temperature are effective chiefly through giving rise to a condition in the central nervous system that causes exaggerated responses to sensations of heat or cold.

22. Benedict, F. G., and Parmenter, H. S.: Am. J. Physiol. **87**:633, 1929.

23. Bazett, H. C.: J. Physiol. **36**:414, 1908; Am. J. Physiol. **70**:412, 1924; Physiol. Rev. **7**:531, 1927.

He assumes, for example, that a fall in temperature in the central nervous system gives exaggerated responses to the sense of cold, thereby, causing a warming of the body; whereas, a rise of temperature in the same area, gives exaggerated responses to the sense of warmth, leading to a general cooling of the body. In other words, the optimum brain temperature for reflexes giving rise to cooling and warming are not identical.

It is impossible in an article of this scope to do justice to the literature and investigations that have been made in this interesting field of work. I can only mention facts brought out by many investigators that show the importance and complexity of the heat regulating mechanism. Further discussion is beyond the scope of this article. What I wish most to emphasize are the facts that an abnormal rise in temperature in a given organ is damaging to the health and functional activity of the organ; that an abnormal rise of body temperature, in general, is damaging to the health and activity of the subject; and that there is a remarkably effective and complex mechanism which provides under normal conditions for the adequate cooling of both individual organs and the whole body. What I should like to draw attention to subsequently is that defective heat regulation may cause a variety of disorders affecting the body as a whole or affecting the functioning of one of the internal organs, and finally, and most startling of all, may cause abnormal responses in one of the three important cooling surfaces —that is, the skin and the mucous membranes of the nose and the bronchial tree and may cause in these localities serious pathologic changes.

The literature on the heat regulating mechanism was completely summarized in important papers by Barbour,[7] Bazett,[23] and Cannon and his associates,[2] and to these the reader is referred for a detailed discussion of the subject.

FEVER

When the rate of heat production exceeds the rate of heat elimination, the temperature rises, and there is fever. Fever, as observed in the infectious diseases, is not always attributable chiefly to increased production of heat. It is caused often by reduced elimination of heat. This is evidently a fact, for the increased metabolic rates, such as are observed in malaria and typhoid fever, are not nearly so high as those observed with exercise or overeating. Furthermore, in some of the infectious diseases associated with fever, the metabolic rate is actually reduced.

It is stated in many of the textbooks on the practice of medicine and therapeutics, and probably correctly so, that in febrile conditions the heat regulating mechanism is working at an abnormally high level, so

that responses to a normal body temperature would simulate those normally caused by a reduced temperature, and give rise to a retention of heat. In harmony with this view, it is found that the skin of patients with fever is frequently hyperesthetic to cold. In the same way, one might account for the subnormal temperature so frequently observed during convalescence from febrile diseases by assuming that the heat regulating mechanism is then working at an abnormally low level so that normal temperature under these conditions would give rise to the responses normally caused by heat.

These points of view are interesting in relation to the discussion that is to follow, since I believe that many of the cases of so-called noninfectious coryza, bronchial asthma, urticaria and other dermatoses are caused by a defect in the heat regulating mechanism and frequently have their date of onset during or following an acute febrile disease. To account for the condition, one might assume that the usual level at which the heat regulating mechanism works during a period of fever or during a period of convalescence is maintained indefinitely or permanently and might cause the patient, thereafter, to be abnormally sensitive to the effect of heat or of cold or to the effect of both combined.

ACCLIMATION AND DECLIMATION

Healthy persons tolerate climates that vary tremenduously in temperature of the air and moisture of the air. A rapid change in the location of sick persons from one extreme to another, however, may result seriously. Through gradual change, the same patients might become so acclimated as to tolerate the new conditions without gross ill effect. Races become so acclimated to extreme conditions that they live in comfort in atmospheres that prove injurious to newcomers. Persons visiting the tropics sweat much more than the natives. Vernon [24] noticed evidence of acclimation in experiments on muscular work in warm rooms. Bazett [23] noticed it in students kept in warm moist chambers for periods of one hour after ten or twelve exposures. Persons living in the temperate zones feel the effect of the first hot days of spring and early summer more than they do the hotter days of later summer. Likewise, they notice the effect of the first cold days of winter more than they do the colder days later in the season. Finally, persons who have been exposed for an hour or more to cold notice the effect of heat more than they do if they have not been thus exposed. Likewise, persons who have been exposed for an hour or more to heat notice the effect of cold more than they do if they have not been exposed to heat.

---

24. Vernon, H. M.: J. Physiol. **17**:277, 1894; Brit. M. Research Council Rep. **73**:116, 1923.

These well known facts are referred to because under pathologic conditions, the behavior of a person under the influence of a change of temperature is so much more extreme than that referred to that it causes him to be ill enough to seek the advice of a physician. In these, the effect of acclimation or declimation may be much more marked. For example, certain patients with asthma or pruritus are declimated, or perhaps better expressed, unfitted for the cold days of winter by the prolonged summer heat. They may gain tolerance for cold during the winter months and tolerate it better. Others may be unfitted for the heat of summer by prolonged exposures to cold during the winter months. They may gain tolerance for heat or become acclimated during the summer months. In persons of this type, seasonal weather changes may have serious ill effects that are not noticed in normal persons. This will be referred to again subsequently.

MANIFESTATIONS OF HEAT AND COLD SENSITIVENESS

Certain persons through one or several causes become abnormally sensitive to heat or cold. This fact is so apparent as to need no discussion. Manifestations of sensitiveness to heat or cold are believed to vary depending on the primary cause of the sensitiveness and also on the direct inciting cause of the manifestation. Manifestations in some cases seem an exaggeration of a normal reaction to change of temperature or effort; in others, an inadequate reaction; in others, a pathologic deviation from a normal reaction; and finally, in some, an effort to compensate for a defect that prevents a normal response to change of temperature or effort.

Abnormal responses may be classified as follows:

1. General or constitutional reactions.
2. Reactions referable to one of three cooling surfaces; that is, the skin, the nasal mucous membrane and the bronchial mucous membrane.
3. Reactions referable to an internal organ.

Reactions of sensitiveness to heat or cold vary in intensity, in the quickness with which they appear and in location in different persons. In some patients, the reactions seem chiefly constitutional. Examples of this are heat prostration and the effort syndrome. In others, reactions may be referable chiefly to one of the cooling surfaces. Classic examples of this are thermic coryza, thermic asthma and thermic urticaria or eczema. In others, reactions may be referable chiefly to an organ. A classic example of this may be thermic headache or gastric upset caused by change of temperature or effort. The outstanding feature of all the disorders is that they can be consistently brought out, as the case may be, by heat or effort or cold, and can be temporarily relieved by the reverse condition—that is, in the cases of sensitiveness to

heat by cooling or inactivity, and in the cases of sensitiveness to cold by heat or effort.

Constitutional Manifestations of Sensitiveness to Heat; Relationship to Heat Prostration, the Effort Syndrome and Syncope.—Lewis' effort syndrome is frequently caused by sensitiveness to heat. Patients of this type after effort or exposure to hot, moist air often gave a history of exhaustion, weakness, dizziness, tremor, fainting spells or a tendency to faint, a feeling of oppression in the chest, palpitation, anorexia and nausea or vomiting. One or all of these manifestations may appear consistently as an effect of effort or overheating. Heat sensitive patients of this type are exhausted by effort, especially on hot, humid days. Heat, mental effort or physical effort may each have the same effect on highly sensitive persons. The reaction may be so marked that the patients are unable to tolerate the mental effort of watching athletic contests of of attending to an interesting business deal. Likewise, they may be unable to tolerate the physical effort of climbing up on an examining table quickly. Finally, they may be unable to tolerate as much heat as is encountered in the drinking of a cup of hot coffee or in the placing of their arms in a water bath of 42 C. for thirty seconds. In fact, I had one patient who lost consciousness under a heat test which was so mild that one would have to see before he could believe, and who recovered immediately when cooled by an ice rub on the arms.

The aforementioned triad of causative agents can be demonstrated in almost every case of high grade sensitiveness. In cases of moderate sensitiveness, the effect of the entire triad may not be so apparent. That is, the patient may be more sensitive to heat than to mental or physical effort, more sensitive to mental effort than to physical effort or heat, or more sensitive to physical effort than to mental effort or heat. The three agencies, however, can be demonstrated in a majority of cases of pronounced sensitiveness.

I feel certain that many cases of heat prostration and syncope are due to nothing more or less than heat sensitiveness. Patients who are highly sensitive to heat instinctively avoid heat and avoid effort on humid, hot days. If they are so unfortunate as to be unduly exposed to heat or forced to make an effort in hot, humid weather, they may faint, and in case the exposure is gross enough, may be actually shocked. Severe cases such as this may be diagnosed "sunstroke." An expression such as "overcome with heat" would seem more correct. The condition has nothing to do with the sun, except through heat produced by it. Patients rapidly recover from mild strokes of this kind if they are caused to remain quiet and if they are cooled by the removal of clothing, by an electric fan, or best of all, by the rubbing of the skin with ice.

The identity of the condition described and Lewis' effort syndrome should seem apparent. Lewis mentioned in his classic description of the

effort syndrome that symptoms are often brought to the surface through a change in habit such as that brought about by the drafting and drilling of men who had instinctively sought out sedentary lives. I have found classic examples of effort syndrome in persons who give a history of exhaustion, weakness, dizziness, breathlessness and tremor after effort, and who show exactly the same symptoms while absolutely quiet if they are heated with a hot lamp or a diathermic current, or if they immerse their hands and forearms in a water bath at 42 C. Likewise, their complaint can be immediately relieved by the cooling effect of an ice rub on the arms and chest. Furthermore, these patients can usually tolerate a moderate grade of effort if they are simultaneously cooled.

Lewis made the important observation in his study of the effort syndrome that in a large proportion of cases the symptoms followed an acute infectious disease. This, likewise, is true in my series of cases of heat sensitiveness. A large proportion of my patients who show no definite physical defect can definitely date the time of onset of their symptoms to a febrile disease.

A curious phenomenon can frequently be demonstrated in this type of sensitiveness. Symptoms can be elicited not only by immersing the hands and forearms in a water bath at 42 C., but can be incited in this way even after tourniquets have been applied around the arms above the elbow so tightly that blood can neither enter nor return from the arm. Strange to relate, symptoms brought out in this way can be caused to disappear almost immediately if the forearms are rubbed with ice even if the tourniquets have not been removed. Removal of the tourniquets before or after the application of ice does not materially add to the severity of or relief of their complaint. This observation has caused me to believe that symptoms in heat sensitive patients of this type are in part a response to a sensation of heat, and that the application of ice to the skin is an effective remedy, even though it could not directly lower body temperature. In one patient with urticaria who was so highly sensitive to heat that the immersing of one hand in a water bath at 42 C. would cause generalized erythema, pruritus and urticaria, the immersing of one hand in warm water and the other in cold would have no ill effect—that is, the effect of heat in one area could be immediately neutralized by cold in another area. Furthermore, the effect of heat produced by effort could also be prevented or immediately stopped by the effect of cold on the skin.

Symptoms Similar to Effort Syndrome Caused by Cold and Relieved by Heat.—The manifestations of cold sensitiveness may be identical with the aforementioned symptoms, except that the symptoms may be brought out by cold instead of by heat or effort. Patients of this sort are inclined to seek activity and when active enough, they are inclined to feel healthy. Exposure to cold, however, especially when they are

quiet, may cause symptoms such as exhaustion, weakness, dizziness, tremor, palpitation, oppression in the chest and nausea, and in addition, may cause symptoms referable to one of the cooling surfaces—that is, swellings of the mucous membrane of the nose and bronchial tubes or of the skin, or, in addition, may cause symptoms referable to disorder in one of the internal organs, such as headache or precardial pain.

Symptoms can often be reproduced objectively in persons sensitive to heat or cold by rubbing the skin with ice or by having them immerse their forearms and hands in a water bath at 15 C. In the latter case, symptoms often can be brought out by a cold application to the forearms even if tourniquets are tightly applied around both arms above the elbow. Release of the tourniquets may add little if any to their symptoms. Immersing the arms in warm water or the application of heat to the chest may give relief within a short time. These symptoms like the symptoms of heat sensitiveness seem to occur as a response to the sensation of cold and often can be neutralized by the sensation of heat in another locality.

Symptoms Referable to the Cooling Surfaces—i. e., the Nasal Mucous Membrane, the Bronchial Mucous Membrane and the Skin.—This class of disorders is important and widespread and may appear in heat sensitive persons under the influence of increased production of heat or reduced loss of heat, or in cold sensitive persons under the influence of reduced production of heat or increased loss of heat. They may also appear apparently as a result of a sensation of heat or cold. They can be brought out objectively in the same way in which the constitutional symptoms just described can be brought out—that is, by heat or effort, in heat sensitive patients, and by cold and inactivity in cold sensitive patients.

The nasal symptoms consist of sneezing and swelling of the membranes of the nose with increased secretion of clear mucus. If the condition is perennial and of years' standing, chronic edema of the membranes may lead to infection or polyps or both. If swelling is marked, it frequently causes headache.

The bronchial symptoms consist of a feeling of oppression in the chest, cough, and in the more marked cases bronchial obstruction giving rise to asthma. This is frequently accompanied with expectoration of clear mucus. If the condition is chronic, infection may be superimposed, giving rise to true bronchitis.

The skin symptoms may consist of erythema, itching, urticaria, angioneurotic edema, and if the condition is chronic, one or more of the following abnormalities: desquamation, increased secretion from the skin, thickening of the epidermis, cracking of the skin and occasionally herpetiform eruptions. In patients with chronic sensitiveness, especially in those who have prolonged, delayed reactions, the dermatoses may

assume grave and ugly proportions. Swelling, redness, desquamation, secretion and cracking can render the patient unsightly and most miserable. Infection may be superimposed, giving rise to multiple suppurations. There is one class of patients who have skin as dry as parchment. They never sweat nor can moisture be felt on the skin. One whom I observed had a dry parchment-like rash resembling ichthyosis which was made worse by heat or effort. Patients of this class may be the same as those described in the literature who show wide oscillations in body temperature and who do not sweat. The dermatoses caused by heat or cold sensitiveness may be generalized, may occur in patches or may be confined to the exposed parts. The conditions are diagnosed under a wide variety of terms.

Symptoms Referable to an Internal Organ.—These symptoms are almost too numerous to mention. They frequently appear as a result of the effect of heat or cold or effort. They may appear in persons who seem physically normal. There is in addition a class of patients in whom pathologic changes can be found. In these, symptoms may appear under strain. I believe this accounts for the rapid exhaustion of individual organs observed so frequently in older people with arteriosclerosis. As characteristic examples of this may be mentioned: profound mental exhaustion under the influence of emotional disturbances or mental effort; precardial pain and palpitation under the influence of a little effort; abdominal pain following a little effort; pain in the joints or in the muscles following effort, etc. In cold sensitive patients, the identical symptoms may be caused by cold and prolonged inactivity. These symptoms can often be reproduced under observation by the adequate application of heat or cold and can be relieved by the reverse application.

TYPES OF CASES—RELATIONSHIP TO ACCLIMATION AND DECLIMATION

Among thermic sensitive persons, there are those who are so highly sensitive to heat that the effort of getting up out of a chair quickly may precipitate an attack. Likewise, there are patients who are so highly sensitive to cold that the removal of clothing may precipitate an attack. There are, in addition, patients who are only moderately sensitive or slightly sensitive and who do not react unless considerably exposed. There are, furthermore, persons who have immediate reactions and respond within a few seconds or minutes after exposure, and persons who have delayed reactions. In the latter, the manifestations of the reaction may not appear for many minutes or even several hours after exposure. The latter type of person is unfortunate, for he is not so likely to observe a relationship between cause and effect, and is more likely, therefore, to expose himself unwittingly to extremes that he cannot tolerate. In other words, patients who react promptly are likely

to learn their limitations; whereas patients with delayed reactions frequently do not learn this, and frequently expose themselves to the point of causing a dangerous illness. This type of reaction may result fatally.

Under the topic of acclimation and declimation, the effect of marked changes in temperature on average persons was reviewed. The behavior of many heat sensitive persons is similar to that of average persons, except that it may be much exaggerated. Certain thermically sensitive patients react perennially; others react seasonally. The mere fact that a patient is sensitive to heat does not mean that he is inclined to react only in summer. Also, the fact that he is sensitive to cold does not indicate that he reacts chiefly in winter. The fact is that among heat sensitive patients, one finds some who react perennially, others who react only on the hotter and more humid days of summer, and others who react to heat only after previous exposure to cold. If the latter are chilled, they react as they warm up. Others may react to the first

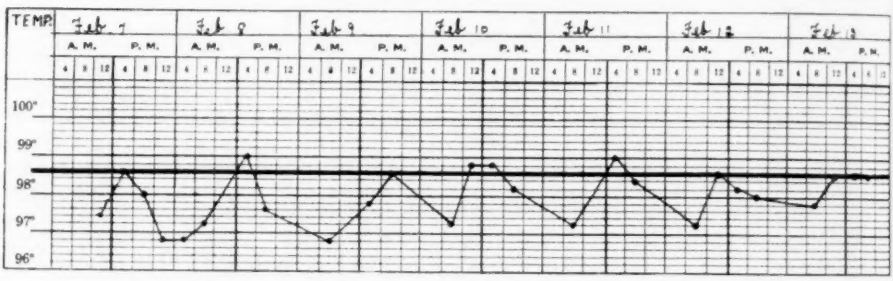

Fig. 1.—The temperature curve in a case of winter urticaria caused by sensitiveness to heat, especially after exposure to cold. Note the typical temperature curve running almost constantly subnormal. When the temperature was raised to normal or a little above by the repeated use of typhoid vaccine, the patient was clinically much better. His sensitiveness to heat, with its manifestation, urticaria, returned after the temperature again fell to its earlier subnormal levels. The basal metabolism was about normal.

warm days of spring after prolonged exposure to the cold of winter. During summer months, they seem to become acclimated to heat and gain tolerance, while during the winter months they become declimated, that is, lose their tolerance for heat. Finally, there is a type of heat sensitive person who reacts after the first cold days of fall or winter. This type seems to lose tolerance for heat under the influence of exposure to the first days of cold weather, and reacts during a warm spell following a cold spell. Likewise, among cold sensitive persons, there are those who react during the coldest days of winter. Some react chiefly in summer. They react to cold most markedly after exposure to heat. During the winter months, they seem to gain

tolerance for cold and cease reacting. In other words, they become acclimated and often tolerate cold better at the height of a winter season than they do at its beginning. They seem to become declimated for exposure to cold by the hot days of summer. Finally there are cold sensitive persons who react to cold chiefly after exposure to the first warm days of spring or summer. They are apparently declimated for cold by the first hot days.

These groups of patients whose reactions I believe are due to the effect of acclimation and declimation confuse the clinical picture and

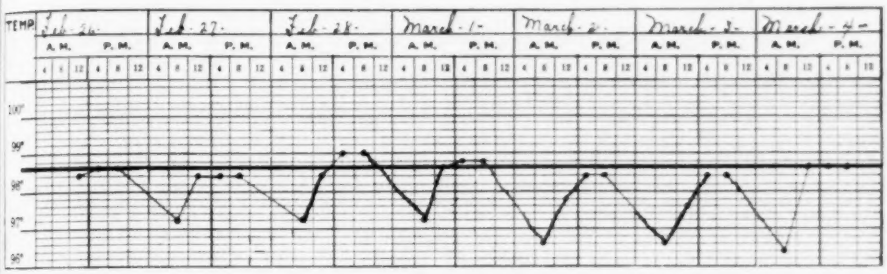

Figure 2

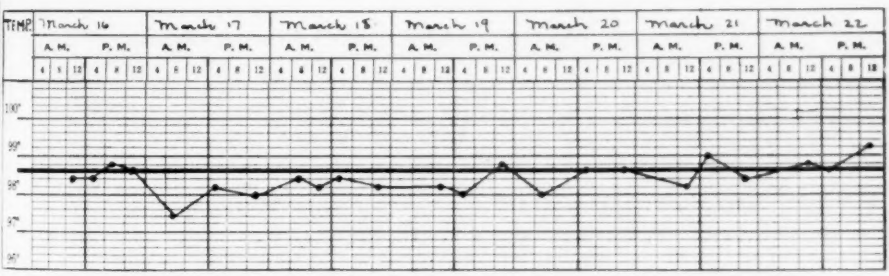

Figure 3

Figs. 2 and 3.—The temperature curves in a typical case of effort syndrome and summer urticaria. In figure 2, the temperature is shown almost constantly subnormal. During periods such as this, if the patient was subjected to heating with a nitrogen lamp or to heating of the forearms and hands with water at 42 C. or subjected herself to a little exertion, mental or physical, she reacted with prostration or an outbreak of urticaria or both. During periods such as that shown in figure 3, when the temperature was kept at a more nearly normal level, the patient could tolerate such degrees of heat as she encountered in her usual activities. The basal metabolism was about normal.

make the patients seem erratic in their behavior toward exposure to heat or cold or effort. The fact is, however, that these patients are extremely consistent in their reactions, in fact so consistent that they

only appear inconsistent. They can be understood after careful study and are then found to react consistently to the conditions of heat, cold or effort to which they happen to be sensitive.

Combined Sensitiveness to Heat and Cold.—The situation is further complicated by the fact that many patients react to body heat most markedly if simultaneously exposed to surface cold. Likewise, other types react to body cold most markedly when exposed to surface warmth, that is, warm, humid air. This condition is commonly observed and confuses the clinical picture. It makes the behavior of the patient seem inconsistent. The fact is, however, that the behavior of these patients also is absolutely consistent. If these patients are studied adequately, they are found to react to the temperature effect to which they are sensitive.

For example, certain asthmatic patients sensitive to heat and effort have reactions only when breathing cold air. They tolerate heat or effort better during the summer months than during the winter months. They tolerate effort better when indoors than when out of doors breathing cold air. A patient of this type may have asthma, if he sleeps in a cold room and uses an excess of cover. He may remain free from reaction if he sleeps in a warm room and uses little cover. In several cases this advice has sufficed to relieve persons with severe chronic asthma. Likewise, cold sensitive persons may tolerate body cold if they are breathing cold air, but may have asthma or a nasal reaction if they breath warm, moist air. Persons of this type are inclined to have attacks following cold baths in the summer. They may tolerate cold baths during the winter months. The cooling of the body by air currents may precipitate attacks if the patient is breathing air which is warm and moist. The patient may tolerate air currents easily, if he is breathing air which is cool and dry.

Whereas, these peculiarities of thermic cases may seem confusing and indefinite, the fact is that the reactions are extremely definite and confuse one only when one does not understand the peculiarities of the type of case under observation.

The reactions described can be reproduced objectively by the appropriate application of heat, cold and effort and can be relieved by a reverse application. This topic will be considered again subsequently.

RELATIONSHIP OF HEAT AND COLD SENSITIVENESS TO INFECTION

In the early part of this work, I quickly learned to my sorrow that in testing patients sensitive to heat and cold, I several times caused them to have febrile attacks that were diagnosed bronchitis or coryza, and in two cases, pneumonia. I quickly learned to be careful in testing patients sensitive to heat and cold and in case of reaction immediately to

reverse the application so as to relieve the condition promptly. Since I have followed this procedure, I have had no ill effects from testing.

These experiences caused me forcibly to realize that patients who are sensitive to heat and cold are more susceptible to infections on exposure to certain changes in temperature than are normal persons. In fact, patients who are sensitive to heat or cold are prone to have one or several febrile attacks each year, occurring usually with the changeable weather in the spring or fall. The reality of this susceptibility can be emphasized, perhaps, through mention of the expression of "catching cold." Normal persons can stand considerable exposure without "catching cold." Heat or cold sensitive persons can often stand little. Heat and cold sensitiveness of mild grade is frequently observed in elderly people, and it is for this reason, I believe, that they "catch cold" so easily on exposure to cold air currents, especially if they have been a little overheated. I think heat sensitiveness and cold sensitiveness are definite factors in the epidemiology of spring and fall colds and pneumonia. Heat sensitive and cold sensitive persons on adequate exposure to changes of weather are prone to become infected. Elderly persons often realize this instinctively, and carefully avoid exposures exceeding their tolerance. Young healthy persons can disregard this.

RELATIONSHIP OF HEAT AND COLD SENSITIVENESS TO ATOPY

The relationship of heat sensitiveness and cold sensitiveness to atopy is interesting. Both illnesses may have the same effect in causing so-called allergic coryza, asthma, dermatoses and allergic shock. When a person is specifically hypersensitive to an agent such as pollen or egg and is also heat or cold sensitive, his symptoms are naturally aggravated greatly if he reacts to the material agent and to heat and cold at the same time.

The reaction to foreign agents such as pollen or egg has, I believe, an unstabilizing effect on the heat regulating mechanism and causes the patient to react more readily to heat or to cold than he otherwise would. It has been found necessary, for example, to be much more careful in the injection of pollen in the treatment of hay-fever and asthma due to pollen, on hot humid days than when the weather is mild. A reaction to pollen is frequently brought to the surface by exercise and heat soon after the patient leaves the physician's office in a state of health. An ice rub applied to the chest and arms is an effective remedy for this type of reaction. In fact, this ranks in its therapeutic effect second only to epinephrine.

The fact that thermic sensitiveness and pollen sensitiveness may occur in the same person and that one of these conditions adds to the ill effect of the other might lead some to believe that the two conditions

are identical; that is, that thermic sensitiveness is caused by atopic sensitiveness. The fact is, however, that the two conditions seem more often distinct and separate. Whereas, both these types of sensitiveness may occur in the same person, this is apparently the exception rather than the rule. Whereas, pollen reactions and thermic reactions may occur simultaneously in a person, they frequently occur at different times of the year; that is, patients may have hay-fever or asthma due to pollen during the fall months and may have identical symptoms caused by thermic sensitiveness during the winter months, when the air is free from pollen.

RELATIONSHIP OF HEAT AND COLD SENSITIVENESS TO HISTAMINE-LIKE BODIES

Since the early writings of Eustis on histamine in relation to the etiology of asthma and urticaria, writers have been attracted by the idea that histamine, if absorbed from the intestinal tract or elaborated internally in excessive quantities, could cause the clinical manifestations of asthma and allied conditions, and they have endeavored to prove this. Since histamine-like bodies, if present in adequate quantities, can cause symptoms similar to those caused by egg in egg sensitive persons or by heat or cold in heat or cold sensitive persons, the simple deduction that egg, heat or cold in certain persons exerts its pathologic effect through the liberation of histamine would be most attractive and might prove correct. This could hardly seem a factor, however, in the patients previously referred to who were caused to react to heat or cold applications on the forearms while tourniquets above the elbow prevented a return of blood from the arm. It could easily be a factor, however, in adding to a reaction caused by egg sensitiveness or due to absorption of histamine because the three conditions give similar symptoms and two or three causes working simultaneously could have a more profound effect on a person than one cause acting alone. The part which might be played by histamine-like bodies in reactions of this type merits all the attention that it may attract. It has been studied recently by Thomas Lewis and by Harris Lewis and Vaughan.

ETIOLOGY AND PATHOGENESIS OF HEAT AND COLD SENSITIVENESS

The study on which this paper is based had been in progress for a number of years before any idea was gained concerning the probable pathogenesis of the condition. It was simply noted that the symptoms enumerated were caused in some patients by heat or effort and were relieved or prevented by cold or rest; while in other patients, the reverse status obtained—that is, identical symptoms were caused by cold or inactivity and could be prevented or relieved by heat or effort.

It was stated in my first communications on the subject [25] that it was believed that the symptoms were due to a disorder in the heat regulating mechanism; in other words, that the patients made a faulty effort to maintain ideal temperature under varying conditions of heat production and heat loss.

Primary Cases.—It has been noticed since then that a large proportion of the patients date the onset of their trouble from an acute febrile disease such as pneumonia, typhoid fever, tonsillar abscess, rheumatic fever or one of the diseases of childhood. This is particularly true of the younger patients, and in these, frequently no definite lesion of any sort can be found on most careful physical examination to account for the disorder, except the history of a febrile disease. I have heard patients say that there seems to be no outward manifestation that a doctor can discover which can account for what they feel within. Usually, such patients seem to be physically perfect, except for the fact that one group cannot stand heat or effort and the other group cannot stand cold or inactivity. They are, unfortunately, often condemned for their inability to carry a burden which they find placed on them.

Secondary Cases.—In a minority of the younger patients, and in many of the older ones who are sensitive to heat or cold, organic lesions can be found which could theoretically play a part in upsetting the normal behavior of the heat regulating mechanism and which might account for their disorders, such, for example, as organic diseases in the nervous system, endocrine disorders, arterial disease, anemia, debilitating diseases, senility or convalescence from a febrile disease. Patients of this class are more likely to receive kindly consideration from their physicians and families.

There are several points at which one could look for disease which might affect the activity of the heat regulating mechanism and cause it to behave badly.

1. In the sense organs and afferent nerve mechanisms which convey the sense of heat or cold to higher centers.

2. In centers in the brain or cord or elsewhere which act as thermostatic regulators of temperature.

3. In the complicated nerve mechanisms that carry efferent impulses from nerve centers which control the caliber of vessels supplying active organs and cooling surfaces; which modify the depth and rapidity of respiration; which control the secretion of moisture on cooling surfaces; also, those that carry impulses which affect the metabolic rate or cause shivering and which might cause one voluntarily to be more active or more quiet and to seek increased or reduced heat loss.

25. Duke, W. W.: Allergy, St. Louis, C. V. Mosby Company, 1925; Urticaria Caused by Light, J. A. M. A. **80**:1835 (June 23) 1923; Urticaria Caused Specifically by Action of Physical Agents (Light, Cold, Heat, Freezing, Burns, Mechanical Irritation, and Physical and Mental Exertion), ibid. **83**:3 (July 5) 1924; Physical Allergy; Preliminary Report, ibid. **84**:736 (March 7) 1925.

4. In end-organs (such as blood vessels, active tissues, surface tissues and secreting structures) which take part in heat regulation.

5. In glands of internal secretion which furnish substances that directly affect metabolic rate and that can also directly affect the caliber of vessels.

6. In the presence of abnormal amounts of histamine-like bodies, which can have an effect similar to that of pollen in pollen sensitive patients or egg in egg sensitive patients and cause reactions similar to those described as caused by heat or cold.

7. Finally, in debilitating diseases, such as anemia, cardiac or renal disease, postfebrile conditions or senility, which weaken the organism as a whole and in this way indirectly interfere with the normal responses to heat or cold.

This series of points at which one might look for trouble is broad in scope. The heat regulating mechanism, however, is exceedingly complex and depends on the coordinated action of many widely separated structures for its effectiveness. A breakdown at any point might alter its normal behavior and cause trouble. Changes at any of these points might theoretically interfere with the normal responses to heat and cold, and through this cause illness. It must be repeated, however, that in a great majority of the younger patients who are highly sensitive to heat and cold, no abnormality can be found to account for the condition except the history of a febrile disease; therefore, one must be satisfied, in many instances, with saying that the heat regulating mechanism is apparently disordered and reacts excessively, inadequately or pervertedly in its response to changes of temperature. I believe the clinical symptoms in the skin and in the nasal and bronchial membranes and, perhaps, elsewhere are due more often to a spasmodic and defective response to change of temperature than to a direct effect of such a change per se on the tissues. The pathogenesis, in this respect, is, I believe, analogous to that of a condition such as cirrhosis of the liver, in which defective efforts at repair do more harm than the primary injury.

EXPERIMENTAL HEAT SENSITIVENESS

I have been able to render tadpoles and minnows sensitive to heat by injuring them with the x-rays. In two series of experiments, each repeated a number of times, a little in excess of an erythema dose of the x-rays was administered to groups of tadpoles and to groups of minnows in shallow dishes of water. After a period of about two weeks, they were tested by placing them in beakers of water and gradually raising the temperature of the water until they were killed. Both the irradiated tadpoles and the irradiated minnows showed little difference in activity as compared with normal controls tested similarly with the rise in temperature until approximately 35 C. was reached. Above this level or thereabouts, each degree of rise had a more pronounced effect on the irradiated animals than on the untreated controls. The treated tadpoles and minnows almost without exception showed disturbed move-

ments or began swimming on their backs or died at a temperature of from 1 to 3 degrees lower than that which affected the controls. Both irradiated and untreated animals were handled identically and at the same time. Reducing the temperature nearly to the freezing point showed less or no difference in the behavior of treated and untreated specimens.

It was concluded that the x-rays so injure young tadpoles and minnows that they cannot adjust themselves so well to a rise in temperature above 35 C. as can the normal, untreated controls.

These experiments were a poor imitation of heat sensitiveness as observed clinically. In the experiments, heat per se apparently did the damage. In the clinical cases, however, the reaction to heat apparently does the harm. The rise of temperature per se is too trivial to account for the profound results that follow an increase in heat or effort.

CLINICAL EVIDENCE OF DISORDER IN THE HEAT REGULATING MECHANISM

Evidence of disorder in the heat regulating mechanism displayed by patients who are sensitive to the effect of heat cold or effort may be summarized as follows:

1. *Unstable Temperature.*—The patients almost always have an unstable temperature. Instead of varying as it does in the average normal person around 98.6 F., with the morning temperature slightly below the evening temperature and with relatively slight change under the influence of the average effort or exposure to heat or cold, the temperature is usually subnormal and frequently is almost constantly subnormal and varies grossly in a majority of cases under the effect of altered heat production or altered heat loss. In the average mild case, the temperature runs between 96.4 and 98 F. Frequently, the temperature almost never reaches normal, and frequently the morning temperature falls as low as 96 or even 95 F. In one extreme case of heat sensitiveness, the morning temperature was occasionally found as low as 92 F. In these patients, a change in temperature of 1 or 2 degrees up or down can often be caused by surprisingly small amounts of effort or by the application of heat or cold to the skin. If the temperature is abnormally low, a hot bath, the application of a hot lamp or the immersion of the forearms in water at 42 C. frequently causes a rise in temperature of from 1 to 2 or more degrees. Conversely, rubbing the chest or arms with ice or immersing the forearms in a water bath at 15 C. for from one to five minutes may cause a drop or occasionally a rise in temperature of 1 or several degrees. These observations have been made a great many times on over 100 heat sensitive or cold sensitive patients, and are remarkably constant. Because of varying degrees of heat production and heat loss encountered in the daily routine of

life in many patients, the variation in temperature is highly variable and erratic—in fact, the temperature curve compares well in irregularities with that in the case of ulcerative endocarditis, except that instead of the irregular, erratic febrile curve of endocarditis, one finds an erratic, irregular subnormal curve. Whereas a subnormal temperature is the rule in heat and cold sensitive patients, some of the latter (cold sensitive ones) run a normal or slightly elevated temperature which is less variable than that found in the heat sensitive patients. For the heat sensitive patients, a subnormal, variable and unstable temperature curve is almost constant, except at odd intervals when they may have febrile attacks. During febrile attacks, they may be very ill, although relieved temporarily of their reactiveness to heat. Frequently, agents that stabilize the temperature and keep it up give marked clinical relief to the patient. For example, asthma caused by heat sensitiveness is almost always relieved during the febrile period of an infectious disease even by the fever caused by pneumonia and in one case by a lung abscess.

2. *Basal Metabolism.*—The basal metabolism is not so easy to study as the body temperature, and in the majority of cases I was unable to demonstrate consistent changes that I could be sure were outside normal variation. However, in a few cases, I demonstrated high grade abnormality and instability in metabolism. In a few cases, the metabolic rate was as unstable as the temperature. I have found it as low as from —40 to —58 on several consecutive days in a patient who seemed physically perfect, except for attacks of itching and urticaria which could be brought out by effort or heat. In one patient, metabolism could be brought up to a normal rate within a few minutes through the effect of a little effort or by the application of a little heat to the skin. It may be said in passing that the outbreaks of hives in this case were believed to be the automatic erratic effort to compensate for the lowered metabolic rate and change of temperature. When the rate was brought to normal, the patient was clinically relieved from urticaria.

It is occasionally observed that the metabolic rate is abnormally high and can be reduced by the application of cold to the skin. Strange to relate, a reduced rate frequently rises after the application of cold to the skin. In many cases, heat and cold may have the same effect so far as change in the metabolic rate is concerned. In some cases, the metabolic rate seems unusually unstable, reacting with ups and downs to a greater extent than it does in normal persons.

Often with a highly pathologic metabolic rate, the temperature may be nearly normal, and vice versa with a markedly subnormal temperature, metabolism may fall within normal limits.

The metabolic rate is not so simple a matter for study in this as it is in thyroid disease. In fact, because of its instability and variability,

I was inclined in my earlier work to believe that the metabolic rate was a minor factor or that I was making frequent errors in my estimations of the rate. This earlier deduction may or may not be correct.

Unfortunately for this study, heat sensitive patients frequently have their pathologic symptoms between midnight and 8 a. m., and at these hours one rarely has the opportunity of studying metabolic rates. Also, frequently when the patients have symptoms, such as asthma, it is not possible because of the nature of the illness to obtain the metabolic rate satisfactorily. Occasionally, I have observed patients with asthma subject to several attacks daily in whom the attack would invariably continue until there was a definite rise or a definite fall in rectal temperature. It would be grossly interesting to know what metabolic change, if any, occurred with this change in symptoms and change in temperature. Such determinations, however, are almost impossible to obtain,

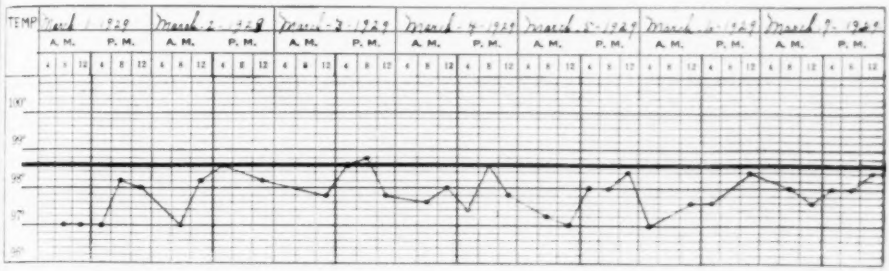

Fig. 4.—The temperature curve of a patient with urticaria of four months' standing caused by sensitiveness to heat. The eruption could be brought out immediately through the effect of heat or effort. This patient, contrary to the rule, showed an endocrine disorder characterized by abnormal length of legs and arms and a metabolic rate that on repeated examination was grossly below normal. On four nearly successive days, it gave such results as —42, —56, —46 and —62. After heating the arms and hands by immersing them in water at 42 C. for five minutes and after heating by a nitrogen lamp applied to the chest for a few minutes, metabolism could be raised nearly to normal—on one occasion from —56 to +16. On one occasion, after an ice rub, from —31 to —4; and on another occasion, from —62 to —9. With the use of glandular extracts designed to raise metabolism, tests a short time after the starting of treatment gave such results as —9, +19, +9 and +19. This was associated with gross clinical relief. Note the irregular, unstable subnormal temperature shown here. There was a total absence of signs of myxedema to account for this patient's lowered metabolic rate.

because the patients during attacks are often so ill that even to get the temperature of the mouth is difficult.

3. *Hyperesthesia to Heat or Cold.*—A number of patients who react abnormally to heat or cold have skin hyperesthesia to heat or cold.

Occasionally, the application of a degree of heat that would scarcely feel more than warm to a normal person feels to these patients as if it might burn or blister. Or, in the case of cold hyperesthesia, an application that might scarcely cause discomfort to the normal person feels so cold to the hyperesthetic patient as to cause him to shudder. A rather large proportion of heat or cold sensitive patients are hyperesthetic to heat or to cold and because of this, instinctively avoid undue exposure.

4. *Reproduction of Symptoms by Application of Heat or Cold and Prevention or Relief by a Reversal of Application.*—The views expressed in this paper are not based on statements made by patients who say that symptoms are brought out by heat or cold, but are based on the fact that the symptoms of which they complain can be reproduced under suitable conditions by the application of heat or cold, and can be relieved by the reverse application. The study is based on a study of patients who were highly sensitive and who reacted immediately. In these, under suitable conditions, the symptoms of which the patient complained could often be elicited and relieved at will by heat, cold or effort. A study of this sort cannot be made on mildly sensitive patients or on patients who give delayed reactions, because of the fact that in these, the results are not sufficiently outspoken to be convincing.

In patients who are highly sensitive to heat, symptoms can be reproduced not only through the application of heat in the form of hot packs, a steam room, a hot lamp, autocondensation current or a diathermic current, but through the effect of heat generated by mental effort or physical effort. In highly sensitive patients, mental or physical effort and heat may give identical results, although in some the maximum effect is produced by one or the other of these three agencies. For example, one of the most highly sensitive patients whom I have examined, could be thrown into an attack of superficial urticaria by the application of a nitrogen lamp to the arm for thirty seconds, by the drinking of a cup of warm water, by heating electric currents, by the effort of leaning over and straightening up several times or by mental effort such as can be elicited by an interesting business deal or by watching an athletic contest. These reactions could be immediately stopped or prevented by the simultaneous application of cold, such as by the air from an electric fan, or by placing the hands in cold water, or by rubbing the arms with ice or by having the patient keep motionless for a time. In other patients highly sensitive to heat, in whom the clinical manifestation was effort syndrome, bronchial asthma or coryza, attacks of effort syndrome, asthma or coryza, as the case may have been, could be brought out by similar applications.

In cold sensitive patients, the reverse status obtained. The patients were benefited instead of made ill by heat or effort. In certain cold

sensitive cases, for example, urticaria could be brought out by immersing the forearms in cold water. In others, asthma or nasal reactions could be brought out through the same agency. The reactions could be relieved or prevented by the application of heat or through effort. Patients of this type feel their best during periods of high grade activity and when warm.

BEHAVIOR OF PATIENTS SENSITIVE TO HEAT AND COLD

Sensitiveness to heat or cold has an interesting effect on the behavior of the afflicted persons. Heat sensitive persons instinctively try to avoid heat and effort. They seek sedentary lives and quiet. They may give the appearance of laziness and may get rattled and hopelessly incompetent when hurried or hot. Cold sensitive persons, on the other hand, may be the reverse, seeking activity both in their business lives and in their games. It is not rare to find cold sensitiveness in highly active, energetic people. I have observed three cases of this sort in polo players. Such patients are completely rid of their troubles during the excitement and effort of a polo game and may have recurrences of symptoms between periods and when they cool off.

It is unfortunate for a patient to change a status in life that he has instinctively chosen and found compatible with his make-up. For example, during the war, many heat sensitive men were drafted and on being drilled in the hot sun, collapsed. In many instances, unfortunately, they were believed to be shirking their duties because on examination nothing could be found to account for their collapse. Lewis relieved this situation greatly by his classic description of the effort syndrome.

Cold sensitive persons who have instinctively chosen a life of activity are unfortunate if necessity forces them into environments where they are cold or inactive for prolonged periods of time. This was notably the case in a patient who was forced into prolonged inactivity by the illness of her husband. The illness that she had when I saw her had actually become more serious and more disagreeable than that suffered by her husband. She obtained immediate relief when she was caused to resume her previous life of activity. I might guess that Napoleon was cold sensitive. It could account for his life of excessive activity, his failures during periods of inactivity and his frequent prolonged hot baths. Frequent cold baths would have been disagreeable for him but more beneficial ultimately. Through this agency he might have gained a very useful tolerance for cold.

Heat sensitive persons often move slowly and methodically, and do things well if allowed time, but collapse or fail if hurried. On the other hand, cold sensitive persons may work best when pressed for time, and often fall down badly if the work before them is not lively enough to keep them adequately active.

THE TERMS HEAT SENSITIVENESS AND COLD SENSITIVENESS

I have used terms in this discussion which can be rather loosely used and which do not commit one to a theory. I do not believe at this stage in the development of this study that stricter terms or restricted definitions can be used. It seems evident that in persons who are sensitive to the effect of heat, cold or effort there are a number of different underlying pathologic conditions that give rise to identical clinical manifestations.

In this paper, therefore, I have employed the terms about as follows: "Heat sensitiveness" has referred to patients who were apparently made ill by an increase in body heat whether this was produced through reduced heat loss, external addition of heat or the generation of heat by mental or physical effort. Patients who responded to increased heat and effort most markedly after previous exposure to cold were considered, in spite of this history, as heat sensitive. Also, persons who responded most readily to heat or effort when breathing cold air were referred to as heat sensitive.

"Cold sensitiveness" was used in referring to patients who were made ill by body cold whether produced by increased loss of body heat or through reduced production of heat as the result of mental or physical inactivity. Cold sensitive persons occasionally reacted most markedly in a hot environment; that is, on cooling off after exposure to heat. These appeared, nevertheless, to be made ill by the immediate effect of cold and were therefore classed as cold sensitive. Furthermore, patients sensitive to the effect of body cold who reacted most markedly while breathing warm, moist air, were called cold sensitive.

In view of the fact that some heat sensitive persons react after previous exposure to cold and that some cold sensitive persons react most markedly after previous exposure to heat, and that many react most markedly to internal heat if subjected to surface cooling and vice versa to internal cold if subjected to surface heat, it might seem simplest in a large proportion of cases to refer to the condition as combined sensitiveness or to refer to the condition under the still less committal term "thermic sensitiveness."

DIAGNOSIS

The diagnosis of thermic sensitiveness is not difficult if one is acquainted with the subject matter described in this paper. The history is important, that is, a history of symptoms such as those mentioned which are brought out by heat or effort or which are brought out by cold or inactivity, and which tend to be relieved by the opposite states. Patients can be tested with heat, cold and effort so that their symptoms can be reproduced during well periods directly under observation. This tends to make the diagnosis objective.

After an impression of a case is gained by history, an effort can be made to reproduce symptoms in heat sensitive cases by immersing the hands and forearms in a water bath at 42 C., or by the application of the heat of a large nitrogen lamp to the chest and arms or by diathermic currents. In case of suspected cold sensitiveness, an effort can be made to reproduce symptoms by having the patient immerse his arms and hands in a water bath at 15 C. or through rubbing his arms and chest with ice.

If these applications are not adequate to reproduce symptoms, further tests can be made in heat sensitive patients by trying simultaneously the effect of heat and physical exercise or by placing the patient in a steam room and having him exercise.

For the testing of combined sensitiveness to heat and cold, a hot lamp can be applied to the chest and simultaneously a large pack filled with cracked ice can be applied to the face in such a way that chilled air can be inhaled. If this application is inadequate, an effort can be made to reproduce symptoms by having the patient exert himself physically while in a refrigerator breathing chilled air. The reverse application is easier to apply—that is, the rubbing of the chest, arms and back with ice while the patient is breathing air through a warm moist pack on the face.

If symptoms are reproduced by one of these applications, relief can usually be obtained in a short time by reversal of the application.

These tests can cause coryza, bronchitis or pneumonia if applied too severely. This complication can be prevented if reactions are stopped immediately by reversing the application that caused reaction.

TREATMENT

The treatment of patients highly sensitive to body heat and effort is likely to be a serious problem. The treatment of patients sensitive to body cold is likely to be brilliant or at least successful.

Treatment of Persons Sensitive to Heat.—Patients who are highly sensitive to heat should avoid effort unless they can be adequately cooled. They should avoid situations in which they are likely to be overheated. They are likely to do best in a dry, cool climate. Even a dry, warm climate may be better for them than a cool, humid climate. Dry air makes body cooling easier. Heat sensitive patients can stand more effort in a dry atmosphere than they can in a humid atmosphere. It may be necessary for them to seek an environment and career that will enable them to lead a quiet life in a dry atmosphere. This may be the best solution in cases of extreme sensitiveness.

In cases of moderate sensitiveness, relief can frequently be obtained through attention to the general health and through the use of agents designed to keep body temperature running at a higher level. Common sense practice of medicine is useful in the less severe cases. Since a

large proportion of the patients react most markedly when the body temperature is lowest, the avoidance of high grade subnormality in temperature is important. Many of the patients are definitely benefited through the effect of fever. A febrile disease almost always gives temporary relief and frequently prolonged relief. Fever can be given artificially through the subcutaneous or intravenous injection of colon bacilli. Through the use of this with gradually increasing doses carried on for a period of one or several weeks and increased to the point of giving frequent febrile reactions, I have been able to effect clinical relief

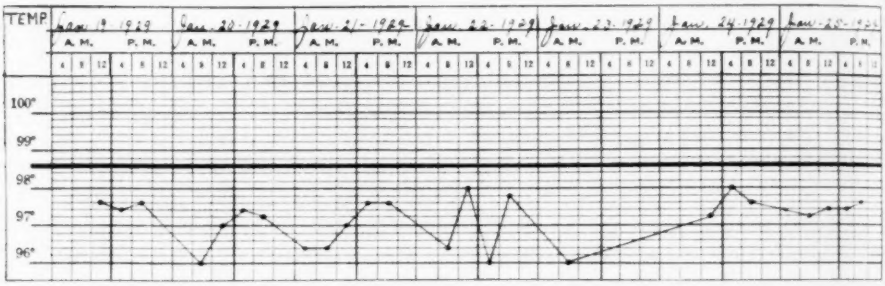

Figure 5

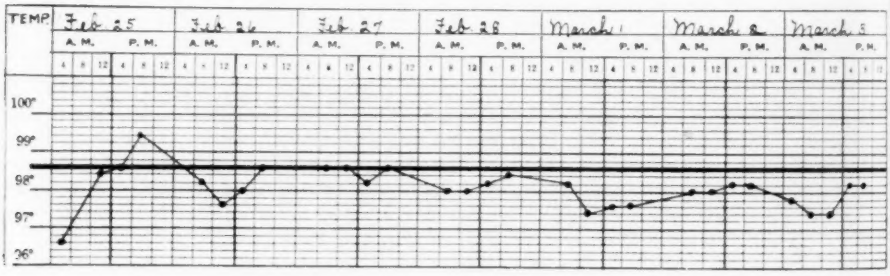

Figure 6

Figs. 5 and 6.—The temperature curves in a case of generalized seborrheic dermatitis present summer and winter without remission for several years, caused apparently by sensitiveness to heat. Note in figure 5 that the temperature curve was almost constantly subnormal. This was typical of the periods in which the eruption was active. Through heat or effort, the patient could be made definitely worse. With the use of heroic doses of *Bacillus coli* designed to raise body temperature to a higher level and frequently above normal, the eczema completely disappeared. The resulting level of temperature is shown in figure 5. In figure 7, note the generalized dermatitis, photographed as darkness of the skin. This photograph was taken at a period when the temperature was running almost constantly subnormal and the eruption active. Note in figure 8 the lighter color and the reappearance of hair and eyebrows after relief from the condition, brought about, I believe, through elevation of the body temperature. The basal metabolism was relatively normal.

in several desperately afflicted patients who had been ill for a number of years. The intravenous use of colon bacilli is likely to give a quick febrile attack even if given in doses as small as 10,000. Although I have had no unfortunate results with this form of therapy, I think the subcutaneous use of colon bacilli is much safer. It has to be pushed boldly, however, for a successful result. I do not wish to recommend this arbitrary method of treatment too strongly, but I can frankly say that I believe some of the therapeutic results that follow the use of

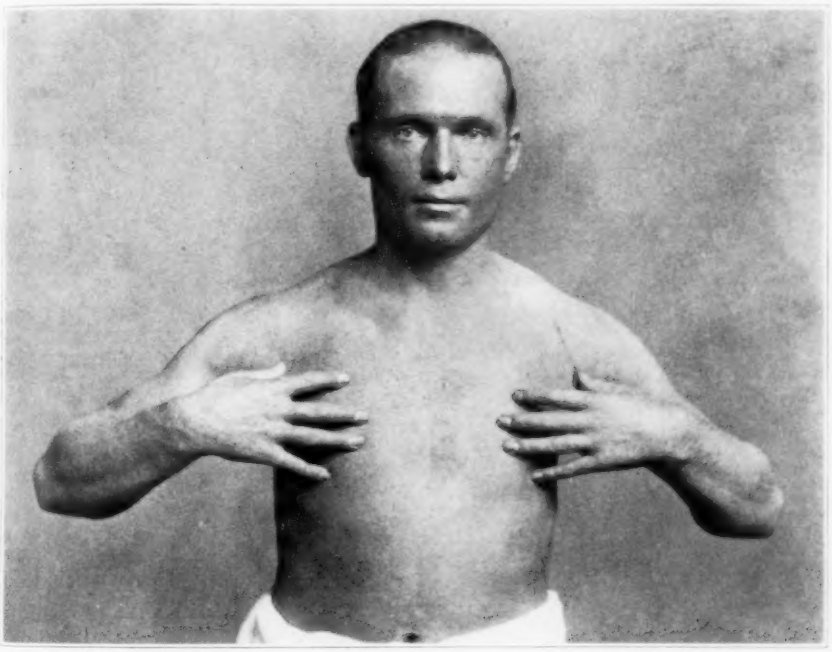

Fig. 7.—The patient with generalized seborrheic dermatitis referred to in figures 5 and 6. Note the pigmentation of the skin and the loss of hair and eyebrows. The patient had for several years been a victim of chronic scaly, weeping eruptions which had constantly resisted therapeutic measures.

autogenous vaccines, peptone and milk in the treatment of persons with noninfectious coryza, asthma, eczema and hives frequently owe their beneficial effect to the elevation of body temperature from subnormal toward normal or above normal.

Temporary relief can often be obtained through the use of hot or cold baths given when the patient needs them. Cold baths for the temporary relief of an attack may be effective within a few moments

and may give a sensational result. Hot baths at midnight for the prevention of a drop in temperature from relatively normal to high grade subnormality during the early morning hours may prevent attacks. I have several times been able to prevent early morning attacks through warming up the patient thoroughly by a hot bath at midnight.

Symptomatic remedies that are useful for symptoms such as coryza, asthma, urticaria and pruritus are epinephrine, pituitrin, ephedrine,

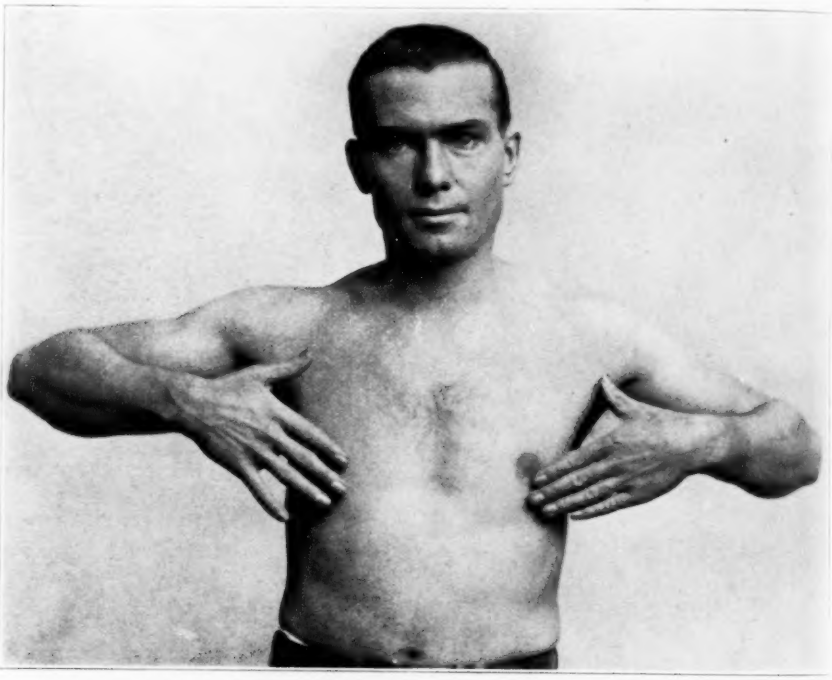

Fig. 8.—The patient shown in figure 7 after the use of therapeutic measures that elevated the body temperature toward normal or a little above.

atropine and the salicylates. Morphine and alcohol may be effective. The former is rarely justified. Acids are indicated if achylia is found.

Cold Sensitiveness.—Cold sensitive patients are much more fortunate than heat sensitive patients. In the first place, it is much easier to avoid overcooling than it is to avoid overheating. If a person is chilled, he can frequently relieve himself through exercise.

Cold sensitive patients, like heat sensitive patients, tolerate changes of temperature in a dry climate better than in a moist climate. Dry air,

whether hot or cold, is easier for them to tolerate than humid air. They should be cautioned against undue exposure to cold.

Fortunately, patients can frequently gain tolerance for cold through the use of frequent cold baths. This is often a most useful remedy in a proved case of cold sensitiveness. Frequently, one can effect complete clinical relief in a cold sensitive patient through so simple a measure as having the patient take a cold bath each morning. A cold bath for fifteen to thirty seconds frequently repeated may suffice to give tolerance. Cold sensitive patients are frequently hyperesthetic to cold. In this case, they may be unable to tolerate adequate exposure to cold during the early part of their treatment. After a time, they are likely to learn to enjoy exposure to cold. Frequently, patients tolerate a rapid rub with ice better than a cold bath. If the ice is moved rapidly enough over the skin, it does not cause a disagreeable sensation of cold. Ice

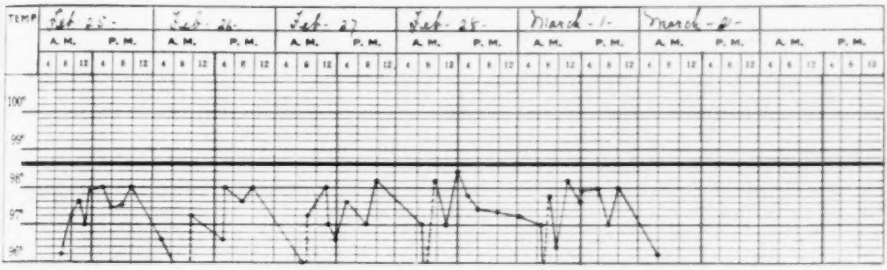

Fig. 9.—The temperature curve in a case of asthma caused by cold sensitiveness. The rises shown by the dotted lines were caused by a little exercise or by the application of heat in the form of a hot bath. If the temperature was raised each morning in this way, the patient remained comfortable throughout the day. If the temperature was not elevated in this way, he was subject to asthma which appeared on his being cooled or after prolonged quiet on his part. These attacks could be relieved immediately through exercise or the external application of heat, if these measures were used soon enough. This patient kept himself constantly comfortable through exercise, a hot bath and a cool shower taken soon after arising.

should be applied over the entire body and the rub should be completed, if possible, within less than one-half minute.

Symptomatic remedies suggested in the treatment of heat sensitive persons can be used to advantage in the treatment of cold sensitive patients. Also, if body temperature is inclined to be subnormal, the patient can frequently be benefited through the use of agents that raise temperature.

SUMMARY

In this paper are enumerated a series of relatively common illnesses which rather frequently are caused, I believe, by disorder in the heat

Fig. 10.—Case of summer dermatitis of face and neck of many years' duration caused by sensitiveness to heat. This eruption could be reproduced within a few minutes during the well period in the winter by immersing the arms in a water bath at 42 C. for less than five minutes, even though tourniquets were applied around the arms above the elbow so tight as to prevent a return of blood flow to the body. The itching, edema, and redness of the skin of the face caused in this way would disappear within a few moments if ice were applied to the forearms before removal of the tourniquets. The patient was relieved of summer dermatitis by spending the summer in an atmosphere which was cool and dry.

regulating mechanism. These illnesses included heat prostration, the effort syndrome, noninfectious coryza, asthma, urticaria, dermatoses and other miscellaneous ailments.

The heat regulating mechanism is important and extremely complex and for effectiveness requires the coordinated action of many structures that control heat production and heat loss. Of structures that seem important may be mentioned sense organs and cerebral centers that have a thermostatic effect on heat control; several hormones that effect both heat production and heat loss; histamine-like bodies that effect vascular tone; three important cooling surfaces, namely, the mucous membrane of the nose, the bronchial membrane and the skin; structures that control the secretion of moisture on cooling surfaces, and structures that control the depth and rapidity of respiration and the rate of blood flow to surfaces and to active internal organs.

I believe that under certain conditions this complicated mechanism is disordered at some point, and when disordered gives abnormal responses to sensations of heat and cold. Responses to heat and cold may then be inadequate to maintain ideal temperature, or exaggerated or in some cases perverted. Abnormal responses to change of temperature give rise more often, I believe, to pathologic changes than does any direct effect of a change in temperature on the tissues themselves.

Allergic reactions to foreign substances may give rise to symptoms similar to those of sensitiveness to heat or cold and may therefore add to the manifestations of heat and cold sensitiveness or in some instances may cause sensitiveness of this type for the time being.

In many persons, adequate cause for heat and cold sensitiveness can be discovered. In others, no pathologic process can be found, except abnormal responses to heat or cold. In this case, one frequently finds a history of an acute febrile disease just antedating the onset of the illness. It is generally stated in textbooks, and I believe correctly so, that in febrile diseases the heat regulating mechanism works at an abnormally high level so that responses to normal body temperature simulate those normally caused by reduction of heat. This gives rise to a retention of heat and a rise in temperature. In many instances, convalescence from an acute febrile disease is associated with a subnormal temperature for a varying period of time. I think that one can assume likewise, therefore, that during the period of convalescence from a febrile disease, the heat regulating mechanism is frequently working at an abnormally low level, so that a response to normal body temperature might simulate that normally caused by increased temperature and give rise to an unusually great loss of heat with a resulting fall in temperature.

It seems possible that under certain conditions the abnormal level at which the heat regulating mechanism works during a febrile disease

or during convalescence is maintained and gives rise to abnormal responses to heat and cold for prolonged periods of time or permanently. In many patients so afflicted, symptoms caused by heat and effort are identical while in others, symptoms caused by cold and inactivity are identical. In patients such as these, the ailments of which they complain can usually be reproduced objectively by the adequate and suitable application of heat and effort or by cold and inactivity.

During reactions of the types described caused by heat and cold sensitiveness, many patients are hypersusceptible to infection. It is believed that this type of sensitiveness plays a part in the susceptibility of many patients to the spring and fall epidemics, and finally in the complicating infections that often follow febrile diseases and in the predisposition of elderly people to respiratory infections.

The diagnosis of the condition can be made by history and practical tests.

The treatment of the condition is described in the text. It may be brilliantly successful in certain types of cases.

AREA OF THE BODY SURFACE AND MEASUREMENTS OF THE NORMAL HEART IN CHILDREN

II. ROENTGEN STUDY *

R. W. KISSANE, M.D.
COLUMBUS, OHIO

In the preliminary report,[1] the necessity of finding a variable that has a close correlation with the size of the heart was emphasized, and the area of the body surface was suggested, because it includes other variables, such as height, weight, age, sex and diameter of the chest, when persons of ideal weight are used as a standard.

Smith and Bloedorn [2] used the area of body surface as a variable to determine the size of the heart, because the former is an index of the mass of actively functioning tissue. They expressed disappointment at the observations, because the individual measurements were scattered over a wide range, which was probably due to the presence of a number of persons in their series whose weights were above ideal; but even then, the range was less than it was when weight was used as a variable.

To determine the size of the heart for an area of body surface of less than 1.5 square meters, 100 children, between the ages of 3 and 14 years, with normal hearts and electrocardiograms, were measured.

METHOD

The height and weight without clothing was obtained in each case. Roentgenograms were made at a distance of 6 feet and measured for the transverse diameter of the heart and the diameter of the chest.

The cases were classified as to their relation to ideal weight for a given height and age, the table of Woodbury [3] being used for subjects under 5 years of age, and the table of Baldwin and Wood [4] for those above this age. For the determination of the area of body surface, the table of Benedict and Talbot [5] gave the best results.

* Submitted for publication, June 10, 1929.

* From the Departments of Cardiology, White Cross Hospital and Children's Hospital.

1. Kissane, R. W.: Area of the Body Surface and Measurements of Normal Hearts, Arch. Int. Med. **42**:135 (July) 1928.

2. Smith, H. W., and Bloedorn, W. A.: The Size of the Normal Heart: A Teleroentgen Study, U. S. Navy Med. Bull. **16**:234 (Feb.) 1922.

3. Woodbury, R. M.: Children's Bureau, U. S. Department of Labor.

4. Baldwin, B. T., and Wood, T. D.: Unpublished, Continental Scale Works, Chicago.

5. Benedict and Talbot: Pub. 302, Carnegie Institution, Washington, 1921, p. 61.

Besides the actual area of body surface in each case, the ideal weights were also determined for those who were 10 per cent above the ideal weight. They were classified into groups with a class interval of 0.1 square meter (table 1), and the mean and range of each class interval were established; this was also done for the children of ideal weight and for those under ideal weight, and a comparison was then made (table 2).

TABLE 1.—*Cases Grouped According to Surface Area*

Number	Body Surface Area	Ideal Weight Surface Area	Height, Cm.	Weight, Kg.	Ideal Weight, Kg.	Age, Years	Sex†	Chest Diameter, Cm.	Heart Transverse Diameter, Cm.
1	0.566	0.657	96.5	12.7	15	3	♀	15.4	7
2	0.566	0.657	96.5	12.2	15	3	♀	15.8	7.7
3	0.597	0.686	104.1	13.6	16.3	3	♀	16	7.8
4	0.597	0.872	119.3	13.6	22.2	6	♀	18.9	8.9
5	0.627	.....	124.3	14.5	....	8	♀	18.8	9.2
6	0.686	0.796	115.5	16.8	20.4	8	♀	17.8	8
7	0.657	0.769	111.5	15.4	19	5	♀	18.6	8.7
8	0.686	0.742	110.4	16.8	18.6	6	♀	17.5	7.5
9	0.627	0.714	105.4	14.5	17.7	4	♀	16.5	8.5
10	0.645	.....	101.6	15.2	....	4	♂	17	8.5
11	0.616	.....	100.3	14.7	....	3	♂	16.8	7.7
12	0.616	.....	91.4	14.5	....	3	♂	15.8	8.2
13	0.657	0.999	127.7	15.6	27.7	9	♀	18.8	8.6
14	0.645	0.74	106.6	15	17.7	4	♂	16	8.2
15	0.686	0.769	111.5	16.3	19	6	♀	16.6	7.9
16	0.686	.....	109.2	16.8	....	5	♀	17.6	8
17	0.686	.....	110.4	16.3	....	4	♀	17.8	7.8
18	0.796	.....	120.6	20.6	....	7	♀	17.5	6.2
19	0.769	0.879	116.8	18.6	22.7	6	♂	18	9.4
20	0.769	0.879	116.8	18.8	22.7	7	♂	18.6	9.7
21	0.769	.....	113.3	19.3	....	6	♀	17.6	8.9
22	0.74	.....	109.2	17.2	....	5	♂	18.8	8.5
23	0.769	.....	104.1	18.1	....	5	♂	16.5	9.5
24*	0.797	.....	100.3	19.5	....	4	♂	17.8	8.5
25	0.797	0.982	121.9	19.3	24	8	♂	18.6	8.7
26	0.74	.....	106.6	17.7	....	4	♂	18.3	8.5
27	0.769	.....	109.2	18.1	....	7	♂	17.4	8.8
28	0.714	.....	104.1	17	....	6	♀	17.5	8.6
29	0.74	0.825	111.5	17.7	20	4	♂	18.4	8.6
30*	0.797	.....	106.6	19.7	....	5	♂	18.3	8.1
31	0.742	.....	111.3	18.6	....	6	♀	17.3	8.3
32	0.74	.....	106.6	17.2	....	6	♂	18.3	7.8
33	0.769	.....	106.6	18.1	....	5	♂	17.4	9.5
34	0.742	.....	112.4	18.1	....	7	♀	15.5	7.6
35	0.796	.....	118.1	20.4	....	8	♀	17.5	8.8
36	0.796	.....	119.3	20.4	....	5	♀	16.5	8
37	0.769	.....	111.5	18.1	....	5	♂	18	8.9
38	0.711	.....	106.6	16.8	....	5	♂	18.4	9.2
39	0.872	.....	125.7	22.9	....	9	♀	18.3	9.1
40	0.853	0.958	124.3	21.1	25	10	♂	19	9.6
41	0.872	.....	124.3	22.7	....	6	♀	18.1	8.4
42	0.845	.....	121.9	21.1	....	8	♀	19.2	9.2
43	0.872	.....	121.9	22.7	....	7	♀	20.6	9.5
44	0.825	.....	118.1	20.4	....	7	♂	19.3	9.1
45	0.853	.....	116.8	21.8	....	6	♂	19.4	9.2
46	0.898	1.048	131.8	23.8	29	10	♀	20	7.9
47	0.872	1.035	130.8	22	27.7	7	♂	20.2	9.9
48	0.872	0.949	128.2	22.7	25.9	8	♀	17.5	8.5
49	0.845	.....	119.3	21.3	....	6	♀	18.5	9.4
50	0.845	.....	121.9	21.1	....	8	♀	21.6	9.2
51	0.879	1.009	128.2	22.5	26.3	11	♂	20.1	10.2
52	0.872	0.949	127	22	25.9	8	♀	20	8.9
53	0.879	1.009	128.2	22.9	26.3	7	♂	20.6	9
54	0.879	.....	130.6	22.7	....	6	♂	21.4	10.8
55	0.853	1.009	127	21.8	26.3	8	♂	19	10.1
56	0.853	.....	121.9	21.3	....	6	♂	18.7	9
57	0.825	.....	120.6	20.4	....	8	♀	17.4	8.8
58	0.879	1.009	127.6	22.7	26.3	8	♂	19.7	8.7
59	0.974	.....	125.7	26.1	....	8	♀	19.8	9.5
60	0.924	.....	124.3	24	....	5	♀	19.6	8.9
61	0.949	.....	124.3	25	....	7	♀	18.7	9.7
62	0.906	.....	123.1	23.6	....	7	♂	18.6	8.6

TABLE 1.—*Cases Grouped According to Surface Area—Continued*

Number	Body Surface Area	Ideal Weight Surface Area	Height, Cm.	Weight, Kg.	Ideal Weight, Kg.	Age, Years	Sex†	Chest Diameter, Cm.	Heart Transverse Diameter, Cm.
63	0.974	1.142	140.9	28.1	33.6	11	♀	18.2	8.9
64	0.974	.....	133.3	26.8	26.8	10	♀	18.9	9.7
65	0.924	1.024	131.8	24.3	28.6	7	♀	19.1	9.7
66	0.924	0.999	127.7	24	27.7	9	♀	18.6	9.8
67	0.949	1.048	134.6	25.9	30.9	10	♀	20.2	7.9
68	0.924	1.134	137.1	24	31.8	7	♂	19.2	7.9
69	0.949	1.164	142.2	25	34	8	♀	21	9.8
70	0.932	.....	121.9	24	....	7	♂	19.4	10.3
71	0.974	.....	127	26.8	....	6	♀	18.2	8.7
72	0.924	.....	128.2	24.5	....	9	♀	19.3	9.4
73	0.958	.....	127.7	25	....	7	♀	20	9.2
74	0.999	.....	134.6	27.2	....	11	♀	19.4	10.3
75	0.958	1.11	134.6	25.2	30.4	10	♂	19	8.2
76	0.999	1.164	130.7	27.2	34	12	♀	20.1	9.9
77	0.924	1.086	131.8	24.5	29	8	♂	20	9.7
78	1.048	.....	138.4	29.5	....	9	♀	20.8	10.1
79	1.024	.....	130.8	28.1	....	11	♀	20.1	9.5
80	1.024	.....	130.8	28.4	....	8	♀	20.7	9.1
81	1.035	.....	130.8	27.5	....	7	♂	19.9	8.3
82	1.06	1.134	137.1	28.1	31.8	10	♂	19.8	9.6
83	1.095	.....	137.1	31.5	....	11	♂	22.4	10.8
84	1.086	1.202	142.2	29.5	34	8	♂	23.6	9.5
85	1.06	.....	127.7	28.1	....	8	♂	23.4	9.4
86	1.06	1.4	154.9	28.4	43.6	12	♂	21.6	10.2
87	1.11	1.3	148.5	30.9	38.1	10	♂	19.5	8.7
88	1.159	1.254	144.7	32	36.8	12	♂	22.8	10.2
89	1.134	1.254	144.7	31.8	36.3	10	♂	21.6	9.4
90	1.188	.....	142.2	35	....	11	♀	20.3	10.7
91	1.11	.....	137.1	30.4	....	11	♂	22.3	10.5
92	1.142	.....	140.9	33.6	....	10	♀	19.1	10.5
93	1.277	1.4	154.9	39.5	45	11	♀	24	10.2
94	1.254	1.4	154.9	36	45	14	♂	22.6	10
95	1.21	1.33	153	36.3	43.1	11	♀	20.7	9.3
96	1.21	1.33	152.4	36.8	43.1	11	♀	23.6	9.8
97	1.255	1.5	160	38	50.9	14	♀	22.1	8.9
98	1.207	.....	152.3	34.5	....	11	♂	19.8	9.1
99	1.207	1.345	149.2	34.3	40.4	13	♂	22.4	10
100	1.44	.....	160	45.6	....	14	♂	23.4	12.2

* Over ideal weight.
† In this column, ♂ stands for male; ♀, female.

TABLE 2.—*Average and Range of Heart Measurements in Each Group*

Surface Area Group Square Meters		Ideal* Weight, Kg.	Under Weight, Kg.	Entire Group, Kg.
From 0.5 to 0.59	Average	.....	7.8	7.7
	Number	.....	4	4
	Limits	.....	7.0-8.9	7.0-8.9
0.6 to 0.69	Average	8.1	8.2	8.2
	Number	6	8	13
	Limits	7.5-9.2	7.8-8.7	7.5-9.2
0.7 to 0.79	Average	8.4	9.2	8.5
	Number	15	6	21
	Limits	6.2-9.2	8.7-9.7	6.2-9.7
0.8 to 0.89	Average	9.2	9.2	9.2
	Number	11	11	20
	Limits	8.4-10.8	7.9-10.2	7.9-10.8
0.9 to 0.99	Average	9.4	9	9.2
	Number	10	8	18
	Limits	8.6-10.3	7.9-9.9	7.9-10.3
1 to 1.09	Average	9.5	9.7	9.6
	Number	6	4	10
	Limits	8.3-10.8	9.5-10.2	8.3-10.8
1 to 1.19	Average	10.5	9.4	10
	Number	3	3	6
	Limits	10.5-10.7	8.7-10.2	8.7-10.7
1 to 1.29	Average	9.6	9.6	9.6
	Number	2	5	7
	Limits	9.1-10.2	8.9-10	8.9-10.2
1 to 1.39	Average	.....	.....	.....
	Number	.....	.....	.....
	Limits	.....	.....	.....
1 to 1.49	Average	12.2	.....	12.2
	Number	1	.....	1
	Limits	12.2	.....	12.2

* Only three cases in this group; therefore these averages were not used.

The cases of under ideal weight were subdivided into subgroups according to what the area of body surface would have been if the weight had been ideal (table 3). These figures were compared with the mean and range in the various class intervals of the ideal weight group, the entire group and one another.

TABLE 3.—*Groups the Children Would Be Classified in if of Ideal Weight for Height and Age*

Groups, Sq. Meters		0.6 to 0.699	0.7 to 0.799	0.8 to 0.899	0.9 to 0.999	1 to 1.09	1.1 to 1.19	1.2 to 1.29	1.3 to 1.39	1.4 to 1.49	1.5 to 1.59
0.5 to 0.599	Average, cm.	7.5	...	8.9	...	...	...	...	...	...	...
	Number	3	...	1	...	...	...	...	...	...	...
	Range, cm.	7-7.8	...	8.9	...	...	...	...	...	...	...
0.6 to 0.699	Average, cm.	...	8.1	...	8.6	...	...	...	...	...	...
	Number	...	6	...	1	...	...	...	...	...	...
	Range, cm.	...	7.8-8.7	...	8.6	...	...	...	...	...	...
0.7 to 0.799	Average, cm.	...	...	9	8.7	...	...	...	...	...	...
	Number	...	...	3	1	...	...	...	...	...	...
	Range, cm.	...	...	8.6-9.7	8.7	...	...	...	...	...	...
0.8 to 0.899	Average, cm.	...	...	...	9	9.3	...	...	...	...	...
	Number	...	...	...	3	6	...	...	...	...	...
	Range, cm.	...	...	...	8.5-9.6	7.9-10.2	...	...	...	...	...
0.9 to 0.999	Average, cm.	...	...	...	9.8	9.1	8.9	...	...	...	...
	Number	...	...	...	1	3	5	...	...	...	...
	Range, cm.	...	...	...	9.8	7.9-9.7	7.9-9.9	...	...	...	...
1.0 to 1.09	Average, cm.	...	...	...	...	...	9.6	9.5	...	10.2	...
	Number	...	...	...	...	...	1	1	...	1	...
	Range, cm.	...	...	...	...	...	9.6	9.5	...	10.2	...
1.1 to 1.19	Average, cm.	...	...	...	...	...	...	9.8	8.7	...	...
	Number	...	...	...	...	...	...	2	1	...	...
	Range, cm.	...	...	...	...	...	...	9.4-10.2	8.7	...	...
1.2 to 1.29	Average, cm.	...	...	...	...	...	...	...	9.7	10.1	8.9
	Number	...	...	...	...	...	...	...	3	2	1
	Range, cm.	...	...	...	...	...	...	...	9.5-10	10-10.2	8.9

TABLE 4.—*Relationship of Transverse Diameter of the Heart to Weight*

Number of Cases	Weight, Kg.	Average Transverse Diameter, Cm.	Number of Cases	Weight, Kg.	Average Transverse Diameter, Cm.
2	12	7.3	3	27	9.5
2	13	8.3	6	28	9.5
4	14	8.4	2	29	9.8
4	15	8.5	2	30	9.6
6	16	8	2	31	10.1
5	17	8.4	1	32	10.2
8	18	8.9	1	33	10.5
4	19	8.2	2	34	9.5
5	20	8.7	1	35	10.7
7	21	9.5	3	36	9.7
10	22	9.3		37	...
2	23	8.2	1	38	8.9
6	24	9.3	1	39	10.2
5	25	8.9	1	45	12.2
4	26	9.2			

Age, sex (table 9), weight (table 4), height (table 5) and the diameter of the chest (table 6) being used as variables, the mean transverse diameter of the heart for each class interval was determined and compared with the curves in this study, the area of body surface being used as a variable, and with the curves of other investi-

gators, Lincoln and Spillman's [6] age and sex curves, and Ziskin's [7] age and height curves (tables 7 and 8).

In order to find the mean transverse diameter of the heart and the range for each class interval of the body surface area from 0.5 to 2.1

TABLE 5.—*Relationship of Transverse Diameter of the Heart to Height*

Number of Cases	Height, Inches	Average Transverse Diameter, Cm.	Number of Cases	Height, Inches	Average Transverse Diameter, Cm.
1	36	8.2	8	50	9.1
...	37	...	8	51	9.2
2	38	7.3	4	52	9.2
2	39	8.1	3	53	8.8
1	40	8.5	5	54	9.7
3	41	8.6	3	55	9.7
7	42	8.5	3	56	10
5	43	8.1	2	57	9.8
6	44	8.4	3	58	9.2
2	45	8.1	...	59	...
5	46	8.2	2	60	9.5
6	47	9.1	3	61	10.1
7	48	9.2	...	62	....
7	49	9	2	63	10.5

TABLE 6.—*Relationship of Transverse Diameter of the Heart to the Chest Diameter.*

Number of Cases	Chest Diameter, Cm.	Average Heart Transverse Diameter, Cm.
4	15–15.9	7.6
7	16–16.9	8.2
15	17–17.9	8.4
25	18–18.9	8.8
18	19–19.9	9.3
15	20–20.9	9.5
5	21–21.9	9.8
6	22–22.9	10
4	23–23.9	10.2
1	24–24.9	10.2

TABLE 7.—*Ziskin's Age Curves*

Age	Number of Cases	Transverse Diameter, Cm.
4	12	8.71
5	17	8.51
6	39	8.64
7	20	9.05
8	80	8.91
9	49	9.25
10	48	9.38
11	57	9.59
12	20	9.85
13	28	9.86
14	24	10.38
15	26	10.24
16	10	10.4

6. Lincoln, E. M., and Spillman, R.: Studies on the Hearts of Normal Children, Am. J. Dis. Child. **35**:791 (May) 1928.

7. Ziskin, Thomas: Development of Size of the Heart in Children, as Revealed by Teleroentgen-Ray Measurements, Am. J. Dis. Child. **30**:851 (Dec.) 1925.

square meters, this group of 100 children was added to the group of 438 men reported by Cohn [8] and Smith [9] and used in the preliminary report.[1] The following groupings were made and compared: the entire group, the entire male group, the males of ideal weight and the female group. A comparison was now made between the boys and girls with the area of body surface as a variable.

COMMENT

If the one case in the class interval from 1.4 to 1.49 square meters is disregarded, and the mean transverse diameter of the hearts in the

TABLE 8.—*Ziskin's Height Curves*

Height, Inches	Number of Cases	Transverse Diameter, Cm.
From 38 to 41	14	8.37
41 to 44	35	8.52
44 to 47	56	8.58
47 to 50	77	9.1
50 to 53	80	9.38
53 to 56	59	9.58
56 to 59	43	9.7
59 to 62	30	10
62 to 65	17	10.5
65 to 68	14	10.7

TABLE 9.—*Relation of Transverse Diameter of the Heart to Age and Sex*

Boys			Girls	
Number of Cases	Average Transverse Diameter, Cm.	Age, Years	Number of Cases	Average Transverse Diameter, Cm.
2	7.9	3	3	7.5
5	8.4	4	2	8.1
6	8.9	5	4	8.4
5	9.2	6	9	8.5
10	9	7	5	9
6	9.3	8	11	9
..	...	9	5	9.4
5	9.1	10	4	9
3	9.9	11	8	9.9
2	10.2	12	1	9.9
1	10	13	..	...
2	11.1	14	1	8.9

entire, under ideal and the ideal weight groups, with the area of body surface as a variable, is compared (table 2), the curve of the entire and the ideal weight groups is found to be the smoother, thereby showing good correlation, while the under ideal weight curve is more irregular. When the 438 adult males are combined with these cases and studied with regard to ideal weight, it is apparent that those in the ideal weight group have a smoother curve and better correlation than those in the entire group, the male group or the female group.

8. Cohn, A. E.: An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method, Arch. Int. Med. **25**:499 (May) 1920.

9. Smith, B.: Teleroentgen Measurements of the Hearts of Normal Soldiers, Arch. Int. Med. **25**:522 (May) 1920.

Since the range in the entire group of children is the largest (table 2), and the ranges in the ideal and under ideal groups are practically the same, increase in weight causes an increase in range as it does in adults.

A curve of the mean transverse diameter of the hearts, with height as a variable, and a class interval of 1 inch, is irregular (table 5), which shows poor correlation, especially as compared with Ziskin's [7] height curve for children (table 8); but this is due to the use of a larger class interval, 4 inches, which tends to make a smooth curve.

The curve with weight as a variable and a class interval of 1 Kg. is also irregular (table 4), which shows poor correlation. When the children are grouped according to sex and age is used as a variable (table 9), the curve shows a fair correlation of the mean transverse diameter of the heart, but not as good as that reported by Ziskin,[7] and the size of the heart of the girls is smaller than that of the boys at any given age, thereby disagreeing with the observations of Lincoln and Spillman [6] that until the age of 7 the hearts of girls are smaller than those of boys, but that after 11 years of age, this condition is reversed.

A curve of the mean transverse diameter of the heart with the diameter of the chest as a variable and a class interval of 1 cm. shows good correlation (table 6). The area of body surface and the diameter of the chest have a closer correlation to the size of the heart in children than age, height, weight or sex, and age has a closer correlation than height or weight; but since the area of body surface incorporates these other variables, and has the same relation to the size of the heart in children and adults, it is a clinical criterion for the estimation of the size of the normal heart with the best general correlation.

CONCLUSIONS

Cases of ideal weight for height should be used in the estimation of the measurements of normal hearts.

Cases of over or under ideal weight for height have an antagonistic influence on the close correlation of the area of body surface with the mean transverse diameter of the heart.

Increase in the weight of children as a group increases the range from the mean transverse diameter of the heart, with the area of body surface as a variable.

In this series of children, the mean transverse diameter of the hearts in girls was smaller than that in boys at any age. The area of body surface has the same close correlation to the size of the heart in children as in adults.

THE MECHANISM OF SECONDARY ANEMIA*

A. H. DOUGLAS, M.D.
AND
H. TANNENBAUM, M.D.
NEW YORK

Three mechanisms may be concerned in the production of anemia: (1) hemorrhage, (2) diminished production of blood or impaired delivery of erythrocytes from the hematopoietic tissue into the circulation and (3) destruction of blood. One might add hydremia, as, judged by the ordinary methods of clinical investigation, it would appear to be anemia.

In order to decide which of the aforementioned factors is active in the production of the common forms of secondary anemia, we attempted to determine whether in those conditions there is an abnormality in the formation or destruction of red blood cells. In this investigation we relied on the fact that the reticulated cell count furnishes the most accurate index of bone-marrow function available, and that the icteric index is a simple and reliable measure of breakdown of hemoglobin, except in patients with hepatic lesions or obstructed biliary passages.

Much work has been done recently both with the reticulated cell count and with the icteric index. The bulk of this work, however, has dealt with one or the other of these values separately. The only reference encountered in the literature involving both determinations is that of Dyke and Greener.[1] These authors reported the values in two cases of pernicious anemia, and demonstrated an increase in reticulocytes and a decreased icteric index during remissions of the disease. It is only with a knowledge of both values that one can classify the forms of anemia accurately and determine the cause in a given case. In table 1 appears the general scheme for such an analysis.

That the reticulocyte count is a reliable measure of the production of red blood cells is fairly well established. Hawes[2] showed that the count is high in childhood (up to 5.7 per cent) and following hemorrhage. Dameshek[3] reported that the count surpasses 6 per cent before clinical evidence of a remission appears in pernicious anemia, and that

* Submitted for publication, June 18, 1929.

* From the Department of Medicine, Cornell University Medical College, and the Second Medical (Cornell) Division, Bellevue Hospital.

1. Dyke, S. C., and Greener, J.: Reticulocyte Crises and Serum Bilirubin in Pernicious Anemia, Lancet **1**:1068, 1928.

2. Hawes, J. B.: A Study of the Reticulated Blood Corpuscles by Means of Vital Staining Methods, Boston M. & S. J. **161**:493, 1909.

3. Dameshek, W.: Reticulated Cells: Their Clinical Significance, Boston M. & S. J. **194**:759, 1926.

death follows repeated low counts. These observations strongly suggest that the appearance of reticulated cells in the circulation is associated with an active erythropoietic function.

As the reticulocyte count is a measure of erythrocyte formation, so is the icteric index a guide to the destruction of red blood cells, or, more exactly, to the breakdown of hemoglobin. The quantity of pigment indicated by the icteric index may include: (1) pigment derived from broken-down hemoglobin; (2) bilirubin further altered by liver cells and excreted into, but reabsorbed from, biliary channels; (3) bilirubin and hydrobilirubin absorbed from the intestine, and (4) food pigments, such as carotin and xanthophyll. The icteric index, of course, is a measure of blood destruction only when there is no injury

TABLE 1.—*The Relation of the Reticulated Cell Count to the Icteric Index*

Reticulated Cell Count	Normal or Low Icteric Index	High Icteric Index
High	Hemorrhage with good bone-marrow response	Destruction of blood with good bone-marrow response
Normal	Hemorrhage with poor regeneration by bone-marrow	Destruction of blood without good bone-marrow response
	Diminished* production of blood or impaired delivery of erythrocytes into the circulating blood	Destruction of blood without good bone-marrow response
Low	Hemorrhage with poor regeneration by bone-marrow	Destruction of blood or hemolytic anemia, with poor regeneration of red blood cells
	Diminished* production of blood during the transition from a higher to a lower number of red cells	Destruction of blood or hemolytic anemia, with poor regeneration of red blood cells
	Hydremia	

* When the output of new red blood cells is diminished, there is a decrease in the number of the younger reticulated cells before there is a corresponding reduction of adult erythrocytes. Hence, during the transition from 5,000,000 red blood cells per cubic millimeter to a lower figure, the ratio of reticulated cells to total erythrocytes is below normal. When a new equilibrium is established at the lower figure, the ratio returns to normal, although the total number of both reticulated and adult cells is low.

to the liver or biliary obstruction. To avoid the presence of food pigments and clouding of the serum by fat, one can draw blood for the determination at a suitable interval after meals, as Bernheim [4] pointed out.

Some prefer the quantitative van den Bergh test to the icteric index. Bernheim, however, showed that the icteric index can be just as accurate and is to be preferred in cases of hypobilirubinemia; she advised that it be used as the simpler procedure.

The blood bilirubin in patients with anemia was studied first in cases of pernicious anemia. In 1917, Blankenhorn [5] reported bile

4. Bernheim, A. R.: Significance of Variations of Bilirubinemia, Arch. Path. & Lab. Med. **1**:747 (May) 1926.

5. Blankenhorn, M. A.: The Bile Content of the Blood in Pernicious Anemia, Arch. Int. Med. **19**:344 (March) 1917.

pigment in the blood in this type of anemia, and since then many writers have demonstrated hyperbilirubinemia in this disease—Perkins,[6] St. George and Brown,[7] Andrews,[8] Hirshfeld,[9] Lepehne[10] and others. Much less work has been done on secondary anemia.

NORMAL VALUES

Normal standards for both determinations discussed have been definitely established. Hawes gave the normal range of reticulated cells as from 0.3 to 1.4 per cent, with 0.85 per cent as the average in fifteen subjects. More recently, Davidson and McCrie[11] gave 0.5 per cent as the average figure, and Krumbhaar[12] stated that from 0.2 per cent to 0.8 per cent covers the great majority of normal persons. The differences in the foregoing figures were probably due to variations in technic, but one may safely take 1.5 per cent as an upper limit and consider higher values as probably abnormal. According to Hawes' limits and the average normal total of 5,000,000 red blood cells per cubic millimeter, the normal total of reticulocytes may be given as from 15,000 to 70,000, with a mean of 43,000.

The normal icteric index varies, according to Stetten's[13] determinations in 144 cases, from 2.5 to 5. St. George and Brown found that in 90.8 per cent of 120 normal subjects the rate fell between 3.5 and 5.5. They quoted similar figures obtained by van den Bergh, Hymans and Snapper.[14] Bernheim's normal limits are from 4 to 6.

The values for serum bilirubin, expressed in milligrams per hundred cubic centimeters, that are given by Schiff,[15] van den Bergh, Hymans

6. Perkin, F. S.: Estimation and Clinical Significance of the Icteric Index, Arch. Int. Med. **40**:195 (Aug.) 1927.

7. St. George, A. V., and Brown, A. L.: Value of Icteric Index in Differentiating Anemia, Arch. Int. Med. **36**:847 (Dec.) 1925.

8. Andrews, C. H.: A Clinical Study of van den Bergh's Test in Jaundice, Quart. J. Med. **18**:19, 1924.

9. Hirschfeld, H.: Ueber die Rolle der Milz in dem Pathogenes der perniziösen Anämie, Ztschr. f. Klin. Med. **87**:165, 1919.

10. Lepehne, G.: Weitere Untersuchungen über Gallenfarbtstoff im Blutserum der Menschen, Deutsches Arch. f. klin. Med. **135**:79, 1921.

11. Davidson, L. S. P., and McCrie, J. G.: Phenomenon of Reticulation and Alteration in Size of Red Blood Corpuscles After Liver Therapy, Lancet **2**:1014, 1928.

12. Krumbhaar, E. B.: Increased Percentage of Reticulated Erythrocytes in the Peripheral Blood, J. Lab. & Clin. Med. **8**:11, 1922.

13. Stetten, De W.: Surgical Value of the Estimation of the Bile Pigmentation (Icterus Index) of the Blood Serum, Ann. Surg. **76**:191, 1922.

14. Van den Bergh, A. A.; Hymans and Snapper: Die Farbstoffe des Blutserums, Deutsches Arch. f. klin. Med. **110**:540, 1913.

15. Schiff, L.: Serum Bilirubin in Health and Disease, Arch. Int. Med. **40**:800 (Dec.) 1927.

and Snapper, Lepehne,[16] McNee,[17] Botzian,[18] Wiemer[19] and others, indicate that 1 mg. is a safe upper limit. This is roughly equivalent to an icteric index of 10,[20] or is somewhat higher than the upper limit of normal given.

METHODS

To investigate the mechanism of secondary anemia, the reticulocyte count and the icteric index of thirty-four patients in the wards of the second medical division of Bellevue Hospital were determined.

The reticulated cell counts were made with the technic described by Hawes and Cunningham,[21] except for a slight modification. This consisted in leaving the blood in contact with the brilliant cresyl blue for from twenty to thirty minutes, instead of the thirty seconds recommended, so as to give more time for the diffusion of the dye and for staining. As evaporation can occur only at the edges of the coverslip, it never was sufficient to cause crenation of the corpuscles in this time. When the counts were being made, the number of reticulated cells was noted while one thousand red blood cells were counted.

Total red blood cell counts were made with the use of standardized pipets and an improved Neubauer chamber. The same chamber was used for all the counts. The hemoglobin percentage was determined with a Dare hemoglobinometer, which had been matched against a Sahli instrument provided with a glass standard. The blood for the three determinations mentioned was drawn from the finger with a single puncture.

The blood for the icteric index was drawn from the median cubital vein within one hour after obtaining the blood for the other determinations; 10 cc. was drawn with a syringe which had been previously rinsed with physiologic solution of sodium chloride to avoid hemolysis. The blood was collected in large cotton-plugged test tubes which were then placed in the icebox. The supernatant serum was used for the determination. The serum was allowed to clear by standing; centrifugating was resorted to only when it was suspected that suspended corpuscles were present, or when the serum was turbid.

Readings were made by daylight with a Duboscq colorimeter in which undiluted serum was compared with the standard set at the 15 mark. Readings were all made within twenty-four hours after the blood was drawn. The standard used was a 0.01 per cent aqueous solution of potassium dichromate to which 4 drops of concentrated sulphuric acid per thousand cubic centimeters had been added to prevent fading.

In this study the intervals of time between meals and the drawing of blood could not be observed, but apparently this did not affect the results obtained.

---

16. Lepehne, G.: Untersuchungen über Gallenfarbstoff im Blutserum d. Menschen, Deutsches Arch. f. klin. Med. **132**:96, 1920.

17. McNee, J. W.: Use of the van den Bergh Test in the Differentiation of Obstructive from Other Types of Jaundice, Brit. M. J. **1**:716, 1922; Jaundice: A Review of Recent Work, Quart. J. Med. **16**:390, 1923.

18. Botzian, R.: Beiträge zur Bilirubingehalt des menschlichen Serums bei Gesunden und Kranken, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **32**:549, 1920.

19. Weimer, P.: Ueber d. Direkte und Indirekte Diazo-Reaktion in Blutserum, Deutsches Arch. f. klin. Med. **151**:154, 1926.

20. Cullen, C.; Emerson, E. E., and Woodruff, W.: Icteric Index, Spectrophotometric and Quantitative Studies, Arch. Int. Med. **41**:428 (March) 1928.

21. Cunningham, T. D.: A Method for Permanent Staining of Reticulated Red Cells, Arch. Int. Med. **26**:405 (Oct.) 1920.

RESULTS

The cases studied may be grouped as follows: (1) secondary anemia with no evidence of hemorrhage or obvious destruction of blood, (2) secondary anemia with hemorrhage and (3) nonanemic subjects, including normal controls.

Twenty-five patients with secondary anemia, none of whom presented evidence of hemorrhage or of conditions known to destroy blood, had normal reticulocyte counts, varying from 0.1 to 1.4 per cent (with the exception of two patients showing 2 per cent), (table 2). The average was 0.85 per cent and the majority were between 0.8 and 1.1 per cent. These figures coincide with the values in normal subjects given by Hawes. The totals varied from 3,000 to 74,000 per cubic millimeter, with an average of 34,000 and a median of from 40,000 to 50,000. The icteric indexes ranged from 2.6 to 15. Elimination of the high indexes in cases of cardiac insufficiency with possible hepatic congestion, gives 2.6 and 8.2 as the limits for twenty cases, with a normal average of 5.3.

In six patients with anemia due to hemorrhage, shown in table 3, the reticulocyte count was normal or high, varying from 1 to 5 per cent. The average, 1.9 per cent, was above the upper limit of normal. The total counts lay within limits of from 20,000 to 130,000 per cubic millimeter, with an average of 61,000. The icteric indexes were normal or low in the uncomplicated cases (from 2.6 to 8). In one case (case 3) giving a high figure there was evidence of injury to the liver, and in the other (case 6) the patient died a few hours after blood was drawn. In case 3 (table 3) the rise in the reticulated cell ratio and total can be followed in repeated counts as the total number of red blood cells increased.

Table 4 includes seven nonanemic subjects. The reticulated cell counts, varying from 0.3 to 1.3 per cent, lie within the normal limits. The icteric indexes range from 4 to 9.6 and include some values slightly above the normal limits set by Bernheim.

COMMENT

In this study, most of the cases fall into the group of secondary anemia without hemorrhage or known hemolytic disease. Very few reticulocyte counts in such cases are available in the literature. The values found here, and recorded in table 2, are within the normal limits obtained by Hawes. They are somewhat above normal if Krumbhaar's figures are accepted. It may be that in this work the longer contact between cells and vital stain increased the number in which the reticulum was made visible. The total number of reticulocytes per cubic milli-

TABLE 2.—*Reticulated Cell Count and Icteric Index in Secondary Anemia with no Evidence of Hemorrhage*

Patient	Sex	Age	Diagnosis	Hemoglobin	Number Red Blood Cells per C.Mm.	Number Reticulocytes per 1,000 Red Blood Cells	Number Reticulocytes per C.Mm. Blood	Icteric Index	Remarks
1	M	..	Syphilitic aortitis, subacute bacterial endocarditis	41	3,980,000	9 (0.9%)	36,000	5.0	
2	M	25	Tonsillitis, arthritis, myositis	65	4,500,000	5 (0.5%)	22,500	5.6	
3	M	..	Grip, infectious arthritis	53	3,670,000	9 (0.9%)	33,000	5.0	
4	M	48	Infectious arthritis, auricular fibrillation	58	3,700,000	14 (1.4%)	52,000	4.6	
5	M	30	Gonococcal arthritis	55	4,350,000	8 (0.8%)	25,000	5.7	
6	M	52	Syphilis, lead poisoning (?)	65	3,500,000	11 (1.1%)	38,500	4.1	
7	M	60	Syphilitic aortitis, decompensation	68	4,380,000	10 (1.0%)	44,000	6.0	
8	M	46	Chronic interstitial nephritis	57	3,520,000	14 (1.4%)	50,000	4.6	Thirteen days before, hemoglobin was 43 and red blood cells 3,510,000
9	M	42	Chronic nephritis, hypertension, cardiac failure	72	3,770,000	3 (0.3%)	11,000	12.0	
10	F	40	Chronic interstitial nephritis	44	2,500,000	3 (0.3%)	7,500	8.2	
11	F	23	Pericarditis	76	5,300,000	11 (1.1%)	58,000	5.3	
12	M	16	Acute rheumatic fever, carditis	55	4,100,000	3 (0.3%)	12,000	4.7	
13	M	23	Rheumatic disease of the heart, polyarthritis	69	4,500,000	4 (0.4%)	18,000	7.0	
14	F	16	Chorea	48	5,400,000	4 (0.4%)	22,000	5.0	
15	M	18	Rheumatic disease of the heart, auricular fibrillation decompensation	65	5,300,000	8 (0.8%)	42,000	14.0	Nine days previously, hemoglobin was 60 and red blood cells 5,170,000
16	..	..	Acute rheumatic fever, endocarditis, fibrinous pleurisy	45	3,270,000	1 (0.1%)	3,000	4.9	
17	F	34	Abscess of the lung (post-pneumonic)	60	3,100,000	10 (1.0%)	31,000	5.8	Ten days previously, hemoglobin was 50
18	M	..	Abscess of the lung	76	4,710,000	10 (1.0%)	47,000	7.8	
19	M	45	Abscess of the lung.	36	2,860,000	20 (2.0%)	57,000	5.5	Two days later, red blood cells were 3,000,000 and hemoglobin 40
20	F	23	Chronic pulmonary tuberculosis	64	4,750,000	6 (0.6%)	28,500	5.0	
21	F	44	Lobar pneumonia	34	3,800,000	5 (0.5%)	19,000	3.0	
22	F	27	Chronic cardiovascular disease	80	4,900,000	2 (0.2%)	10,000	11.0	
23	F	45	Chronic myocarditis, general arteriosclerosis, brachial and facial neuralgia	70	4,700,000	10 (1.0%)	47,000	8.8	
24	M	38	Echinococcus (liver), chronic bronchitis, fibrinous pleurisy, myocarditis	60	3,700,000	20 (2.0%)	74,000	2.6	
25	F	65	Chronic nephritis, general arteriosclerosis, auricular fibrillation, decompensation	55	3,950,000	12 (1.2%)	47,000	1.5	
Average						8.5	34,000	6.6	
Median						8-11	40-50,000		
Excluding cases with cardiac insufficiency, average								5.3	

meter would be more significant, as Johnson and Berglund [22] pointed out, if the trend were known in each case, i. e., whether the number of red blood cells was increasing or decreasing at the time of the count.

TABLE 3.—*Reticulated Cell Count and Icteric Index in Secondary Anemia with Evidence of Hemorrhage*

Patient	Sex	Age	Diagnosis	Hemoglobin	Number Red Blood Cells per C.Mm.	Number Reticulocytes per 1,000 Red Blood Cells	Number Reticulocytes per C.Mm. Blood	Icteric Index	Remarks
1	M	52	Gastro-intestinal bleeding	29	2,000,000	10 (1.0%)	20,000	2.6	
				35	2,528,000	..	.....	3.0	Twenty-one days previously
2	M	40	Carcinoma of rectum	40	3,635,000	16 (1.6%)	58,000	6.5	
3	F	25	Pulmonary tuberculosis, gastro-intestinal bleeding, cirrhosis alcoholic neuritis	48	3,680,000	21 (2.1%)	77,000	16.55	Nov. 20, 1928
				38	1,960,000	..	.....	...	Nov. 6, 1928; reaction to van den Bergh direct test slightly delayed; indirect slightly +
				54	2,320,000	12 (1.2%)	28,000	...	Nov. 9, 1928
				45	3,160,000	18 (1.8%)	57,000	...	Nov. 19, 1928
4	M	46	Bleeding duodenal ulcer	50	3,080,000	14 (1.4%)	43,000	8.0	
5	M	52	Chronic nephritis with edema and hypertension	50	2,700,000	14 (1.4%)	38,000	4.2	Intestinal hemorrhage four days before count
6	M	43	Hemorrhagic pericarditis	35	2,600,000	50 (5.0%)	130,000	10.0	Patient died on day of count
Average						19	64,000	7.9	
Excluding cases 3 and 6, average								5.3	

TABLE 4.—*Reticulated Cell Count and Icteric Index in Nonanemic Subjects*

Subject	Sex	Age	Diagnosis	Hemoglogin	Number Red Blood Cells per C.Mm.	Number Reticulocytes per 1,000 Red Blood Cells	Number Reticulocytes per C.Mm. Blood	Icteric Index
1	F	24	Normal	80	4,850,000	12 (1.2%)	58,000	9.6
2	M	24	Normal	85	5,900,000	4	24,000	7.5
3	M	23	Normal	90	5,420,000	13	70,000	9.6
4	M	23	Normal	75	4,800,000	8	38,000	7.7
5	F	..	Acute tonsilitis, erythema nodosum	84	4,900,000	12	58,000	4.0
6	M	52	Duodenal ulcer (healed)	85	5,300,000	6	32,000	8.3
7	M	69	Chronic bronchitis, general arteriosclerosis	80	5,500,000	7	38,500	5.6
Average						8.8	46,000	7.5

In interpreting the icteric indexes, one must note the statement of St. George and Brown that, in their experience, cardiac insufficiency

22. Johnson, R., and Berglund, H.: Significance of the Reticulocyte as Index of Regeneration in Different Types of Experimental Anemia, Proc. Soc. Exper. Biol. & Med. **25**:517, 1928.

was one of the common disturbing factors which gave a high figure. Omitting such cases from our series, the results for secondary anemia, both with and without hemorrhage, are normal or low. This is in accord with the observations of other investigators. Bernheim [23] reported thirty-three cases of secondary anemia with hypobilirubinemia. St. George and Brown gave the following indexes: carcinoma with anemia, from 1.5 to 3; sarcoma, 1.8; lymphosarcoma, 2; Hodgkin's disease, 2; fibromyoma, 1; ulcerative colitis, 1.5, and gastric ulcer, 3. Perkins found from 1 to 3.5 mg. of bilirubin per thousand cubic centimeters of blood (from 1 to 3.5 icteric index units) in secondary anemia.

To summarize the results for group 1, it may be said that in secondary anemia without hemorrhage or conditions known to destroy blood, a normal reticulocyte count and a normal or low icteric index are found. The type of anemia in this group, therefore, cannot be due to destruction of blood. Hemorrhage having been excluded,

TABLE 5.—*Reticulated Cell Count and Icteric Index in All Subjects Studied*

Cases	Average Number Reticulocytes per 1,000 Red Blood Cells	Average Number Reticulocytes per C.Mm. of Blood	Average Icteric Index
25 cases; secondary anemia with no evidence of hemorrhage	8.5 (0.85%)	34,000	6.6
20 cases of the foregoing group, eliminating those with cardiac insufficiency	...	.....	5.3
6 cases: secondary anemia with evidence of hemorrhage	21 (2.20%)	61,000	7.9
4 cases of foregoing group, eliminating those with hepatic damage	...	.....	5.3
7 nonanemic subjects	8.8 (0.88%)	46,000	7.5

diminished production of blood must be regarded as causal, in spite of the normal reticulocyte count; as has been explained, when equilibrium at the anemic level is achieved, the ratio of reticulocytes to erythrocytes is normal. Hydremia as a factor is to be thought of chiefly in connection with the anemia of nephritis. However, if it were the sole factor in the type of case illustrated by patient 10 (table 2) the volume of blood would have to be doubled. In the anemia of chronic nephritis, however, there is no increase in volume of the blood, judging from the few cases studied by Brown and Roth,[24] Keith, Rowntree and Geraghty,[25] and Bock.[26] These authors did not include cases of chronic

23. Bernheim, A. R.: The Icterus Index (A Quantitative Estimation of Bilirubinemia, J. A. M. A. **82**:291 (Jan. 26) 1924.

24. Brown, G. E., and Roth, G. M.: Anemia of Chronic Nephritis, Arch. Int. Med. **30**:817 (Dec.) 1922.

25. Keith, N. M.; Rowntree, C. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547, 1915.

26. Bock, A. V.: The Constancy of the Volume of the Blood Plasm, Arch. Int. Med. **27**:83, 1921.

nephritis with anemia and without edema. It is possible that in this condition, dilution of the blood is a factor, in spite of the leukocytosis found as a rule in these cases. Points in favor of hydremia are the relatively infrequent association of anemia and edema in cases of chronic nephritis (Brown and Roth), and the demonstration by MacLean [27] of a fall in blood pressure and rise of hemoglobin with increase in the volume of urine in cases of acute nephritis. Hydremia, therefore, cannot with certainty be ruled out as a possible factor in the anemia of nephritis, although it is probably not the chief cause of anemia in that condition.

The diminished production of blood in the type of anemia discussed may theoretically be due to toxic action on, or circulatory changes in, the hematopoietic system. Whatever the mechanism, hemoglobin synthesis is affected more than the production of red cells since the color index is low.

In the five patients suffering from secondary anemia with hemorrhage, the reticulocyte counts were normal or high. This agrees with the observations of others. Hawes' figures have been quoted. Davidson and McCrie stated that hemorrhage may raise the reticulocyte count to 35 per cent. Our highest figure was 5.8 per cent. In none of the cases was the count low.

In these cases the reticulocyte count varied from normal to high according to the response of the bone-marrow to the demands for increased function. As the cells were removed intact from the circulation, there was no reason to expect an increase in the icteric index.

Of the seven nonanemic subjects, two had icteric indexes which were somewhat high—9.6. In other respects, the observations agree with those of other investigators.

SUMMARY AND CONCLUSIONS

1. Cases of anemia may be grouped etiologically if the reticulocyte count and the icteric index are known. They may be classified as due to: (*a*) hemorrhage; (*b*) diminished production of blood, or faulty delivery of the red cells into the circulating blood; (*c*) destruction of blood or (*d*) combinations of these factors.

2. In twenty cases of secondary anemia without hemorrhage, the reticulocyte counts were normal and the icteric indexes normal or low.

3. The common form of secondary anemia found in such chronic conditions as nephritis or abscess of the lung and in some of the acute infections (particularly acute rheumatic fever) is the result of the diminished production of blood.

---

27. MacLean, H.: Diagnosis and Treatment of Renal Diseases, ed. 3, Philadelphia, Lea & Febiger, 1927, p. 19.

TWENTY-FOUR HOUR BLOOD SUGAR VARIATIONS IN FASTING AND IN NONFASTING SUBJECTS *

J. SHIRLEY SWEENEY, M.D.
DALLAS, TEXAS

As the response of the diabetic patients to food is the same as that of the normal person save for the varying degrees of deficiency of endogenous insulin, it was thought that the knowledge of normal fluctuations of the blood sugar over a period of twenty-four hours might prove of value in the management of diabetic cases. There have appeared in the literature studies of blood sugar variations in diabetic and in nondiabetic persons. From these studies suggestions have been offered to facilitate the handling of diabetes as regards the time insulin should be given, the dosage, etc. Jonas and his associates [1] studied all day blood sugar curves in diabetic and nondiabetic persons. They found from their observations that mild cases of diabetes may be controlled by a single morning dose of insulin, owing to the tendency of the blood sugar to be rising or to rise higher after this meal; that two doses are often necessary, in which cases the afternoon dose is usually smaller than the morning dose, and that the lowest blood sugar is usually noted just before the midday meal or in the afternoon. The present study was made for the purpose of confirming in part the aforementioned investigators' observations and to determine the blood sugar variations during fasting over a period of twenty-four hours.

Eight medical students free from organic ailments were used in this study. Four of the students were allowed "general diets" and four were deprived of all food for the twenty-four hours. Blood sugar determinations by the Folin-Wu method were made every two hours throughout the twenty-four hours on both groups. The readings were all made by me. The results of these observations are so uniform that additional observations were considered unnecessary.

In the accompanying table are listed the results in the fasting and nonfasting subjects. The same data are presented graphically in charts 1 and 2. In chart 3 may be seen the composite twenty-four hour curves of the two groups.

---

* Submitted for publication, June 20, 1929.

* From the Department of Internal Medicine, Baylor University.

1. Jonas, L.; Miller, T. G., and Teller, I. A.: All Day Blood Sugar Curves in Nondiabetic Individuals and in Diabetic Patients With and Without Insulin, Arch. Int. Med. **35**:289 (March) 1925.

COMMENT

There are several interesting suggestions to be noted. The first is that in the fasting group the twenty-four hour curve is practically flat. There is a very slight rise beginning in the early morning which con-

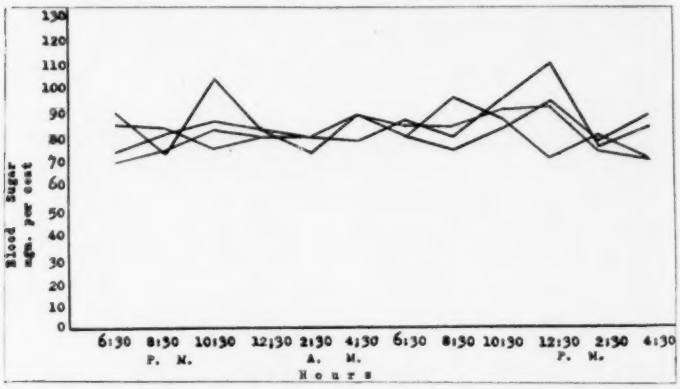

Chart 1.—Two-hourly variations of blood sugars over a period of twenty-four hours in fasting normal persons. (It will be noted in all the charts that the variations appear greater than they really are owing to a rather fine ordinate scale.)

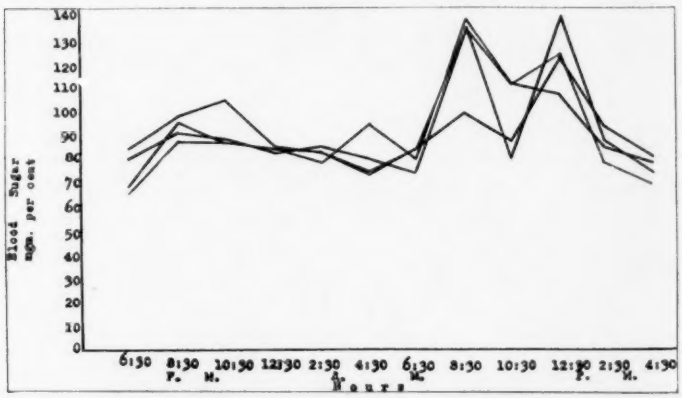

Chart 2.—Two-hourly variations of blood sugars over a period of twenty-four hours in nonfasting normal persons.

tinues to the noon hour and then drops. Although these changes are small, they suggest what may be termed a normal tendency, a conditioned vegetative response so to speak.

In the nonfasting group will be seen a rather insignificant rise following the evening meal, with a subsequent flat curve through the night hours. In the early morning hours, especially following breakfast, occurs a sharp and significant rise followed by a short decline. This is followed by a rise following the midday meal with a subsequent definite drop which is only slightly affected by the evening intake of food.

The explanation and practical significance of these changes are interesting. It has now been shown [2] and well established that food, especially carbohydrates, stimulates the production of endogenous

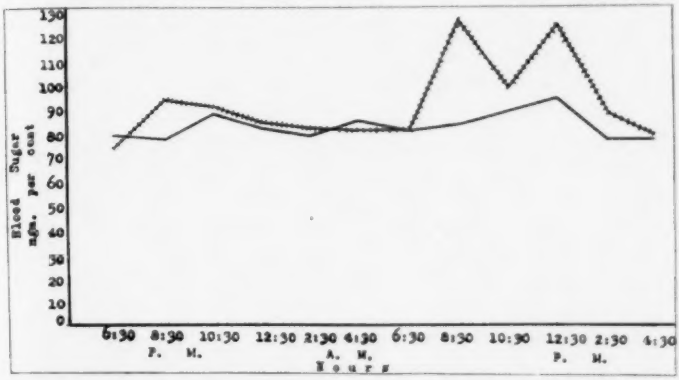

Chart 3.—Average two-hourly blood sugar variations in fasting and nonfasting normal persons over a period of twenty-four hours.

Two-Hourly Variations in Blood Sugar over a Period of Twenty-Four Hours in Fasting and Nonfasting Normal Persons

	Fasting											
	P. M.				A. M.					P. M.		
Subject	6:30	8:30	10:30	12:30	2:30	4:30	6:30	8:30	10:30	12:30	2:30	4:30
1	87	85	77	80	80	79	87	80	95	111	76	83
2	91	79	105	88	74	89	80	74	82	98	78	87
3	73	82	87	83	80	89	80	95	87	71	80	70
4	70	74	88	80	80	89	85	88	90	91	74	69
	Nonfasting											
5	80*	91	89	82	86	80	75	133†	81	141‡	89	77
6	65	87	87	83	78	95	80	138	111	125	80	71
7	83	98	105	85	82	76	83	133	111	108	87	80
8	69	95	83	83	82	75	83	100	89	122	95	83

* Food taken immediately after specimens of blood were taken.
† Breakfast taken about 8 a. m.
‡ Lunch taken about 12:10 p. m.

2. Sweeney, J. Shirley: Dietary Factors that Influence the Dextrose Tolerance Test, Arch. Int. Med. **40**:818 (Dec.) 1927.

insulin. With this knowledge interpretation of the observed changes becomes apparent. At the time the morning food is taken, the pancreatic tissue that has to do with carbohydrate metabolism has been at rest. There has been no stimulation. The effect, therefore, is the same as that observed in fasting persons,[2] namely, a sharp rise in blood sugar due to a sluggish endogenous insulin response. The noon meal is followed by a slightly more active response, and by the time the evening meal is taken, the response becomes more active—as in the case of persons who have been taking meals rich in carbohydrates [2]—and the blood sugar rises to a much lower figure as compared to the morning and noon levels.

The practical significance of these observations is obvious and confirms the conclusions of Jonas and his associates. In very mild diabetes, the blood sugar curve should be kept within normal limits by a single dose of insulin before breakfast. Owing to the "natural" tendency of the blood sugar to rise, this is the safest time for the administration of insulin. By the same reasoning, insulin reactions should be expected to occur in the afternoon or early evening, which is well known to be true by those who treat many diabetic patients.

Deductively, totally or almost totally diabetic patients would have to be treated by several injections of insulin at twenty-four hour intervals. This likewise is a common observation to those who treat patients with diabetes. It follows, therefore, that in treating patients with diabetes one can and should take an optimum advantage of the remaining functioning insulin-producing pancreatic tissue. This can be done with economic and functional advantage to the patient.

CONCLUSION

Twenty-four hour blood sugar curves were made for fasting and nonfasting normal persons. By these studies are explained certain observations noted in the handling of diabetic cases.

It is suggested that by taking into account the normal variations of the blood sugar curve, diabetic patients may be more accurately, satisfactorily and economically controlled.

THE RANGE OF EFFECTIVE IODINE DOSAGE IN EXOPHTHALMIC GOITER

I. THE EFFECT ON BASAL METABOLISM OF REST AND OF THE DAILY ADMINISTRATION OF ONE DROP OF COMPOUND SOLUTION OF IODINE *

WILLARD OWEN THOMPSON, M.D.
Henry P. Walcott Fellow in Clinical Medicine, Harvard Medical School
ALLEN G. BRAILEY, M.D.
PHEBE K. THOMPSON, M.D.
AND
EDWARD G. THORP, M.D.
BOSTON

The normal daily requirement of the body for iodine has never been determined. Indirect evidence on the question is offered by analyses for iodine of soil, water, air and various foodstuffs as they occur in different parts of the world.[1] The foods richest in iodine are certain sea foods, but even these contain only from 0.07 to 2.4 mg. per kilogram, and most foods in the average dietary contain much less. McClendon and Williams [2] found that even in those districts of the United States in which the drinking water is relatively rich in iodine, it would be necessary to drink 10 liters of water daily in order to take in 0.10 mg. of the element by this means.

* Submitted for publication, Aug. 26, 1929.

* From the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital.

* A preliminary report of this work has already been published (Thompson, W. O.; Brailey, A. G., and Thompson, P. K.: The Effective Range of Iodine Dosage in Exophthalmic Goiter, J. A. M. A. **91**:1719 [Dec. 1] 1928).

1. McClendon, J. F.: The Distribution of Iodine with Special Reference to Goiter, Physiol. Rev. **7**:189, 1927. Von Fellenberg, T.: Untersuchungen über das Vorkommen von Jod in der Natur: VII. Ueber der Jodgehalt der Gesteine, der geologischen Formationen und der Mineralien und über die Bedingungen der Jodaureicherung in Erden, Biochem. Ztschr. **152**:153, 1924. Von Fellenberg, T.: Distribution and Circulation of Iodin, Schweiz. med. Wchnschr. **55**:53, 1925. Von Fellenberg, T.: Untersuchungen über das Vorkommen von Jod in der Natur: V. Untersuchungen über den Jodgehalt der Luft, Biochem. Ztschr. **152**:135, 1924. Bourcet, P.: Recherche et dosage colorimetrique de petites quantités d'iode dans les matières organiques, Compt. rend. acad. d. sc. **128**:1120, 1899. Tressler, D. K., and Wells, A. W.: U. S. Bureau of Fisheries, Document 967, 1924.

2. McClendon, J. F., and Williams, A.: Simple Goiter as a Result of Iodine Deficiency; Preliminary Paper, J. A. M. A. **80**:600 (March 3) 1923.

McClendon and Hathaway [3] and von Fellenberg [4] have made valuable measurements of the ingestion and excretion of iodine in normal persons. The first observers, in a three day study of a normal subject, aged 23 years, found that on the average he took in 0.019 mg. and excreted 0.007 mg. of iodine per day. Von Fellenberg did a complete iodine metabolism study on himself, covering a period of fifty-four days. He even analyzed his sweat and nasal secretion for iodine. He maintained himself in iodine balance for twenty-eight days on a daily intake of 0.014 mg., but retained iodine when the intake was increased.

Boothby and co-workers [5] maintained the basal metabolic rate of a "thyroidless individual" at a standard normal level by an average daily intravenous dose of 0.25 mg. of thyroxin, an amount which contains 0.16 mg. of iodine. Certain considerations make it appear probable, however, that this amount of iodine is not necessary to maintain the thyroid gland of a normal man in a healthy condition.[6] The actual dose of thyroxin given was not 0.25 mg. daily, but an average of various doses given at intervals of from two to fourteen days. Some of the injected thyroxin was thus probably destroyed or excreted before it could affect the metabolism, and there is the possibility that iodine atoms from the catabolism of thyroxin are salvaged from the blood by the thyroid and built again into thyroxin molecules. Only in this way would it appear possible for the thyroid gland, particularly in regions where the iodine supply is low, to elaborate the large excess of thyroxin presumably present in exophthalmic goiter.

From a consideration of this evidence, it seems fair to assume that most normal people can maintain a healthy state with respect to thyroid function on a daily intake of iodine which certainly does not exceed, and is probably much less than, the 0.16 mg. of iodine which Boothby and co-workers found sufficient in the form of thyroxin.

In comparison with the almost minute physiologic requirement of iodine in normal persons, the dosage for exophthalmic goiter recom-

3. McClendon, J. F., and Hathaway, J. C.: Iodine Metabolism on Normal Diet in Relation to Prevention of Goiter, Proc. Soc. Exper. Biol. & Med. **21**:129, 1923.

4. Von Fellenberg, T.: Untersuchungen über dem Jodstoffwechsel: I. Versuche mit physiologischen Jodmengen beim Erwachsenen, Biochem. Ztschr. **142**:246, 1923.

5. Boothby, W. M.; Sandiford, I.; Sandiford, K., and Slosse, J.: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects: I. A Method of Studying the Reserve or Deposit Protein with a Preliminary Report of the Results Obtained, Tr. A. Am. Phys. **40**:195, 1925.

6. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: The Calorigenetic Action of Thyroxin at Different Levels of Basal Metabolism in Myxedema, J. Clin. Investigation **7**:437 (Aug.) 1929.

mended by Plummer [7] in 1923 and by Plummer and Boothby [8] in 1924 and widely used since that time in clinics both here and abroad, seems enormous. The drug has usually been given in the form of compound solution of iodine or potassium iodide, in amounts equivalent to 100 to 400 mg. of iodine per day, i. e., at least from 600 to 2,600 times the normal requirement. Observations on the effects of smaller doses seem to be rare. Neisser,[9] in 1920, reported clinical improvement in a few patients with exophthalmic goiter during the administration of as small a dose as from 2 to 5 drops of a 5 per cent solution of potassium iodide three times daily (roughly, from 15 to 38 mg. of iodine daily). His usual routine was to begin with a dose of from 2 to 5 drops three times a day and increase the dose to an "optimum"—sometimes as much as 20 drops three times a day (about 153 mg. of iodine daily). One year later, Loewy and Zondek [10] reported clinical improvement in a few cases from the use of as small a dose as 3 drops of a 5 per cent solution of potassium iodide three times daily (about 23 mg. of iodine daily). In three of their cases they confirmed their clinical impressions with determinations of the basal metabolic rate, although the size of the dose in these three cases is unknown. They usually began treatment with 3 drops of a 5 per cent solution of potassium iodide three times a day and increased the dose to 30 to 40 drops three times a day. Jagić and Spengler,[11] in 1924, reported on the treatment of sixteen thyrotoxic patients with 3 drops of a 5 per cent solution of sodium iodide three times a day (about 25 mg. of iodine per day). In eight patients the condition improved and in two became worse. Cowell and Mellanby,[12] in 1924, stated: "We have not yet determined the minimum quantity of iodide (potassium iodide) that will exert a demonstrable effect, but it is less than half a grain (about 25 mg. of iodine) daily." Cattell,[13] in 1926, recommended that smaller doses than the customary ones be used, and said that 10 minims (0.6 cc.) of compound solution of iodine per day (about 84 mg. of iodine) had proved as satisfactory as larger amounts at the Deaconess Hospital in Boston.

7. Plummer, H. S.: Results of Administering Iodin to Patients Having Exophthalmic Goiter, Society Proceedings, J. A. M. A. **80**:1955 (June 30) 1923.

8. Plummer, H. S., and Boothby, W. M.: The Value of Iodin in Exophthalmic Goiter, J. Iowa M. Soc. **14**:66, 1924.

9. Neisser, E.: Ueber Jodbehandlung bei Thyreotoxikose, Berl. klin. Wchnschr. **57**:461, 1920.

10. Loewy, A., and Zondek, H.: Morbus Basedowii und Jodtherapie, Deutsche med. Wchnschr. **47**:1387, 1921.

11. Jagić, N., and Spengler, G.: Weitere Beobachtungen über Jodwirkung bei Strumen, Wien. klin. Wchnschr. **37**:116, 1924.

12. Cowell, S. J., and Mellanby, E.: The Effect of Iodine on Hyperthyroidism in Man, Quart. J. Med. **18**:1, 1924-1925.

13. Cattell, R. B.: The Elimination of the Iodine in the Urine in Normal Persons and in Exophthalmic Goiter, Boston M. & S. J. **195**:69, 1926.

Wahlberg,[14] in 1926, reported a series of twenty cases in which he gave potassium iodide in doses of from 0.0025 to 0.015 Gm. three times a day (from about 6 to 34 mg. of iodine daily). He obtained a definite remission of the disease in six patients on 0.0075 Gm. three times a day (about 17 mg. of iodine daily). Of these, three were listed as severe, two as moderately severe and one as mild. His tables give no clear evidence that smaller doses were ever effective or that doses twice as large produced remissions when 17 mg. of iodine daily had failed.

In view of the fact that iodine remissions have been produced by doses of such varying size, it seemed desirable to determine, if possible, the range of effective iodine dosage in exophthalmic goiter. We arbitrarily chose to begin with a study of the effect of 1 drop of compound solution of iodine (about 6 mg. of iodine) daily, as even this dose contained what appeared to be a large excess. Since this produced in most cases a maximum reduction in the basal metabolic rate, it was decided to go from this to smaller doses in geometrical progression (½ drop, ¼ drop, etc.). In the present paper we shall consider the effect of 1 drop daily and of larger doses.

METHOD

We observed the effect on basal metabolism of the administration of 1 drop of compound solution of iodine (about 6 mg. of iodine) daily to seventeen unselected patients with exophthalmic goiter who were in the hospital being prepared for operation. Throughout the period of observation, determinations of basal metabolism were made at frequent intervals, usually daily. The routine procedure was to wait until a resting level of basal metabolism was reached. One drop[15] of compound solution of iodine was then administered daily in the metabolism laboratory. When the metabolism again reached a level, much larger doses (usually 30 drops daily) were given. This was done in order to see if any further reduction in basal metabolism would occur, and to prepare the patient more adequately for operation. It is not a method of comparing the effect of large doses with that of small doses. This is shown by the fact that in three of the cases in this paper (charts 2, 3 and 5) the basal metabolism, after showing its maximum reduction on 1 drop daily, began to rise a little; this rise

14. Wahlberg, J.: Das Thyreotoxikosesyndrom und seine Reaktion bei kleinen Joddosen, Helsingfors, Mercators Tryckeri Aktiebolag, 1926.

15. Due to the rough method of measurement, the amount of iodine recorded as being contained in 1 drop of compound solution of iodine is approximate, although it was always measured in the same way, using a dropper of the same size. The iodine was kept in a glass-stoppered bottle. When this solution is kept in a corked bottle, a reaction takes place between it and the cork, as a result of which the cork is slowly destroyed and the solution becomes pale.

continued after the dose was increased to 20 to 30 drops daily. Furthermore, the administration of small doses may interfere with the effect of larger doses administered immediately afterward, as is suggested by the data on the effect of ¼ drop daily in a subsequent paper.[16]

We also observed the effect on basal metabolism of administering 1 drop of compound solution of iodine daily to twenty-three outpatients with exophthalmic goiter. Twelve of these had the disease in mild or in moderately severe form and had received no other treatment. Two had had roentgen treatment for several years before iodine was given. The remainder were patients who had thyrotoxicosis following a thy-

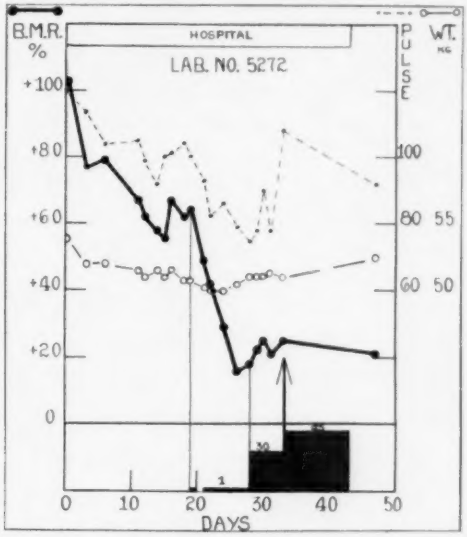

Chart 1.—Marked reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily with no further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter. In this and subsequent charts, arrows denote subtotal thyroidectomies; the black areas represent periods of treatment with compound solution of iodine, the figures above them showing the dosage in drops.

roidectomy (usually subtotal). In no case was medication started or the dosage changed until the existing metabolic level had been confirmed by two or more tests which checked satisfactorily.

16. Thompson, W. O.; Cohen, A. C.; Thompson, P. K.; Thorp, E. G., and Brailey, A. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: III. The Effect on Basal Metabolism of the Daily Administration of ¼ Drop of Compound Solution of Iodine and Slightly Smaller Doses, with a Summary of Results to Date, Arch. Int. Med., to be published.

The Benedict-Roth apparatus and Aub-DuBois standards were used in the determinations of the basal metabolism.

DATA

The results are summarized in tables 1, 2 and 3.

From table 1, it may be seen that in fifteen of seventeen patients (88 per cent) at rest in bed in a hospital, a reduction in basal metabolism of more than 10 per cent was noted during the administration of 1 drop of compound solution of iodine daily. In fourteen of the seventeen

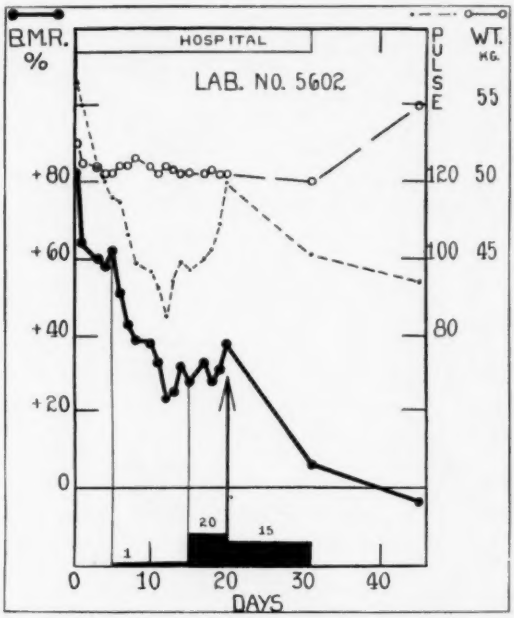

Chart 2.—Well marked reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily, with no further reduction during the administration of 20 drops daily, preceding subtotal thyroidectomy for exophthalmic goiter. In this and charts 3 and 5, a slight rise appeared to start shortly after the maximum reduction in basal metabolism on 1 drop, and to continue on the large dose.

patients, the effect of much larger doses was also noted. In thirteen of these as great a reduction in basal metabolism was obtained with 1 drop daily as with larger doses administered immediately afterward, while one patient showed a greater response during the administration of larger doses. The two that showed no reduction on 1 drop daily did not respond to 30 drops daily. This comparison of the effect of

TABLE 1.—*Summary of the Consecutive Effects of Rest, the Daily Administration of One Drop of Compound Solution of Iodine and of Much Larger Doses Given Immediately Afterward, in Hospital Patients with Exophthalmic Goiter*

Patient				Admission			Rest						On 1 Drop Compound Solution of Iodine Daily							On Larger Doses							
	Laboratory Number	Age	Height, Cm.	Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	No. of Days Before Testing Level Was Reached	Length of Time Effect Was Observed, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Time the Drop Began, Day	Drop in Basal Metabolic Rate in First 24 Hours, Points	Time Required for Maximum Drop, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Size of Dose in Drops, Daily	Total Change in Basal Metabolic Rate on All Doses, Points	Estimated Weight of Thyroid Gland at Time of Operation, Gm.
Mr. J. D'A.	4854	33	165	+ 61	112	55.4	+44	98	54.6	−17	3	3	+19	81	54.9	−25	8	1	−7	12	....	....	....	....	0	30	....	..
Mr. P. O'L.	4888	48	174	+ 57	120	45.7	+49	123	45.5	− 8	1	6	+34	91	44.9	−15	9	3	0	7	+22	93	44.0	−12	15	30-60	−27	95
Mrs. C. G.	4893	49	158	+ 38	124	52.5	+25	104	51.6	−12	1	5	+19	94	50.9	− 7	8	0	0	0	+16	100	50.5	− 3	4	10-30	−10	..
Miss H. R.	4909	17	167	+ 70	134	59.5	+40	104	59.7	−36	2	3	+20	102	57.1	−20	11	1	−5	9	+21	108	57.0	+ 1	3	30	−19	216
Mrs. T. P.	4949	56	149	+ 37	120	51.7	+30	106	51.7	− 7	1	2	+ 8	80	50.2	−22	13	5	0	12	....	....	....	....	..	..	....	..
Mrs. E. G.	4958	53	157	+ 41	88	51.9	+25	76	50.6	−16	3	8	− 5	54	49.9	−30	9	1	−5	5	± 0	59	49.8	+ 5	4	30	−25	40
Mrs. L. DeN.	5059	25	144	+ 57	136	40.5	+44	105	39.6	−13	2	6	+20	85	39.2	−24	9	4-7	0	7	....	....	....	....	..	..	....	..
Mrs. F. H.	5168	26	164	+ 81	119	75.7	+58	109	69.5	−23	2	9	+16	72	67.2	−42	10	3	0	8	+27	82	67.9	+11	7	30	−31	..
Miss E. M.	5272	35	166	+103	120	53.9	+63	99	50.8	−40	11	19	+17	77	51.1	−46	9	1-2	...	6-7	+23	88	51.1	+ 6	5	30	−40	98
Mrs. A. B.	5419	28	156	+ 76	106	43.7	+60	97	42.5	−16	1	6	+26	78	44.6	−34	11	2	0	6	+25	75	45.6	− 1	5	15	−35	..
Mr. W. B.	5475	33	159	+ 64	120	64.3	+49	106	62.5	−15	2	8	± 0	68	66.1	−49	18	2-3	0	11	+ 2	69	68.0	+ 2	9	10-30	−47	85
Mrs. B. W.	5491	44	154	+ 55	146	45.5	+49	111	45.1	− 6	0	3	+22	84	44.0	−27	10	1-2	...	6	+29	89	43.7	+ 7	4	30	−20	..
Miss V. G.	5581	18	160	+ 80	132	49.8	+82	122	47.4	+ 2	0	4	+47	124	44.4	−35	9	..	...	..	+46	129	44.1	− 1	7	20	−36	221
Mr. H. E.	5596	33	172	+ 54	108	47.7	+56	101	47.7	+ 2	0	2	+27	80	47.7	−29	12	1	−11	5	+27	81	48.4	0	3	30	−29	..
Mrs. M. McC.	5602	28	160	+ 82	146	52.5	+60	120	50.4	−22	1	5	+22	94	50.5	−38	10	1	−10	7	+31	104	50.5	+ 9	5	20	−29	54
Mrs. A. F.	5650	45	152	+ 30	120	49.1	+37	95	44.1	+ 7	0	7	+10	80	45.7	−27	10	1-2	...	4	+ 8	80	45.8	− 4	2	30	−29	80
Mrs. A. H.	5741	50	153	+ 36	132	56.3	+17 fibrillating	108	56.7	−19	4-6	20	+17 regular	116	57.4	0	9	0	0	0	+15	112	57.7	− 2	5	30	− 2	..
Average	All patients (17)....			+ 60			+46			−14	2	7	+19			−27	10											
	All who received large doses (14)....			+ 62			+48			−14	2	7.5	+19			−29	10				+21			+ 2	6		−27	
	All in whom the basal metabolic rate dropped 10 points or more (15)			+ 64			+50			−14	2	6	+19			−31	11											
	All in whom the basal metabolic rate dropped 10 points or more and who received large doses (12)....			+ 67			+52			−15	2	7	+20			−32	11				+22			+ 2	6		−30	

TABLE 2.—*Detailed Presentation of the Data on Basal Metabolism Summarized in Table 1**

Patient	Lab. No.	Days Before Starting Iodine											Days After Starting Iodine																											
		11	10	9	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	24	25	26	27	28
Mr. J. D'A.	4854	..	....	....	A	....	....	....	+61	....	+45	+39	+33	+18	....	+22	+13	+24	+19	+18	+33†	....	....	S															
Mr. P. O'L.	4888	..	....	A	....	+57	+48	+45	....	....	....	+53	+49	+46	+38	....	+47	+36	+28	+33	+38†	+27	....	+28	....	+28	+19	....	+27	....	+21	....	...+21	S+21						
Mrs. C. G.	4893	..	....	....	A	....	+38	+26	....	....	+20	+31	+22	+20	+20	....	+18	+17	+19	+17†	....	+15	....	+16	S															
Miss H. R.	4909	..	....	....	....	....	....	A	+76	....	+38	+42	+37	+32	+34	+26	....	+26	+25	+22	+18	+17	+23†	....	+21	S+20														
Mrs. T. P.	4949	..	....	....	....	....	....	A	....	+37	+28	+32	+30	....	+29	....	+25	....	....	+19	+13	....	....	+6	+9	Iodine omitted														
Mrs. E. G.	4938	..	A	+41	....	....	+22	....	....	+34	....	+19	+14	....	+8	....	−3	....	−4	....	−8†	....	....	±0	S±0															
Mrs. L. DeN.	5059	..	....	..	..	....A	+57	+51	+45	+50	+38	....	+43	....	+40	....	+38	....	....	+18	....	+21	....	S																
Mrs. E. H.	5168	..A	+81	....	+63	+52	....	+58	....	....	....	+58	....	+59	+50	+53	+38	....	+24	+14	+19	+16†	+20	+23	....	+26	+35	+30	S	+26										
Miss E. M.‡	5272	..	....	+67	+62	....	+58	+56	+67	....	+62	+64	....	+49	+42	....	+29	....	+16	....	+18†	+22	+25	+21	....	S	+25													
Mrs. A. B.	5419	..	....	....	A	+76	+62	+56	+60	....	+63	+58	+56	+44	+39	+36	....	+23	+27	+25	+30	+27	+25†	....	+27	+24	+25	S	+24											
Mr. W. B.	5475	A	....	+64	+69	+50	....	+49	+49	+50	+50	+47	+48	....	+35	+29	+20	+16	+13	+11	....	+8	+5	+4	....	+2	−3	....	+1	+2†	−4	−3	+2	+7	−1	+8	+2	+3	S
Mrs. B. W.	5491	..	....	....	....	....	....	A	+55	+47	+50	+49	....	+40	+37	+30	+26	+22	+20	....	+22	+25†	+27	+26	+33	S	+31													
Miss V. G.	5581	..	....	....	....	....	A	+80	....	....	+88	+78	....	....	....	....	....	....	+49	....	....	+45†	....	+20	....	....	+50	....	+42	RH										
Mr. H. E.	5596	..	....	....	....	....	A	....	....	+54	+59	+56	+45	+44	+31	....	+24	+22	+19	+25	+33	+39	....	+27†	+27	+28	S	+27											
Mrs. M. McC.	5602	..	....	....	....	A	+82	+64	....	+60	+59	+61	+51	+43	+39	....	+38	+33	+23	+25	+32	+28†	....	+33	+28	+31	S	+38											
Mrs. A. F.	5656	..	....	A	+30	....	+26	....	+36	....	....	+37	....	+25	+27	+10	+14	+12	+8	....	+8	+10†	+10	+6	S	+28													
Mrs. A. H.§	5741	Sore throat	....	....	....	....	....	....	+21	+18	+22	+23	+25	+19	....	+25	+13	+23	+17	+17†	+19	....	+15	+16	+14	S													

* A represents the time of admission to the hospital; S, subtotal thyroidectomy, and RH, right hemithyroidectomy.

† The time of starting larger doses (usually 30 drops daily).

‡ Admission was on the 21st day; the basal metabolic rate was +103, +77 and +79 on the 20th, 17th and 14th days, respectively, before starting iodine. The dose of iodine was forgotten on the second day.

§ Admission was on the 22d day; the basal metabolic rate was +36, +28, +19, +20, +13, +12 and +15 on the 21st, 19th, 17th, 16th, 15th, 13th and 12th days, respectively, before starting iodine.

TABLE 3.—*Summary of the Effects of the Daily Administration of One Drop of Compound Solution of Iodine, and of Larger Doses Given Immediately Afterward, to Outpatients with Exophthalmic Goiter*

Patient	Laboratory No.	Age	Height, Cm.	Before Treatment: Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	After Reaching Level on One Drop of Compound Solution of Iodine Daily: Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	After Reaching Level on Larger Doses: Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Size of Dose in Drops Daily	Total Change in Basal Metabolic Rate on All Doses, Points	Comment
Miss E. D.	316	52	154	+46	91	55.5	+ 4	67	59.9	—42	....	...	....	....	..	....	Roentgen treatment several years before
Mr. J. W.	1812	44	174	+17	92	55.6	— 2	73	55.7	—19	— 2	65	56.7	0	30	—19	Following subtotal thyroidectomy
Mr. F. B.	2205	11	150	+39	108	32.8	+ 4	87	32.7	—35	....	...	....	....	..	....	Roentgen treatment several years before
Mr. O. G.	2375	32	171	+39	86	65.4	+21	64	67.7	—18	+20	66	69.5	— 1	20	—19	Following subtotal thyroidectomy
Mrs. M. R.	3913	24	159	+30	76	48.1	+ 1	68	48.5	—29	— 1	62	49.3	— 2	5	—31	Following subtotal thyroidectomy
Mrs. C. N.	3961	30	159	+28	98	44.2	+ 6	93	46.8	—22	— 3	90	47.1	— 9	45	—31	Following subtotal thyroidectomy
Miss B. P.	3967	16	148	+20	112	52.4	— 2	81	53.7	—22	+ 2	80	53.3	+ 4	5	—18	Following subtotal thyroidectomy
				+12	105	52.6	—10	78	53.8	—22	+ 4	105	48.5	+14	5	— 8	
Mrs. E. O.	4675	35	156	+29	106	47.7	+ 1	85	48.7	—28	—11	87	50.9	—12	30	—40	Preceding operation
Miss E. F.	4694	28	172	+23	83	68.0	— 2	72	72.9	—25	— 4	82	72.5	— 2	10	—27	Following subtotal thyroidectomy
Mrs. I. G.	4758	38	159	+29	103	63.0	+ 2	81	66.1	—27	+12	92	65.9	+10	5	—17	No other treatment
				+19	90	72.1	+10	92	69.1	— 9							
Miss A. Y.	4822	21	165	+72	133	51.7	+28	91	53.0	—44	+18	80	53.2	—10	30	—54	Preceding operation
				+67	118	52.7	+34	93	53.8	—33	+34	100	54.3	0	10	—33	
Mrs. E. F.	4906	28	158	+21	83	45.5	— 1	64	45.7	—22	— 3	64	47.0	— 2	15	—24	No other treatment
Miss E. K.	4935	17	152	+15	100	43.5	+15	94	44.2	0	+ 7	94	45.5	— 8	20	— 8	No other treatment
Mrs. G. G.	4986	25	147	+21	93	62.1	± 0	68	63.5	—21	+ 6	88	67.3	+ 6	10	—15	Following subtotal thyroidectomy
Miss S. G.	5092	18	148	+40	124	42.9	+26	96	43.9	—14	....	...	....	....	..	....	No other treatment
Mrs. E. H.	5168	27	164	+44	107	88.5	+ 8	74	92.0	—36	....	...	....	....	..	....	Following subtotal thyroidectomy
Miss E. M.	5272	35	168	+43	94	61.3	+23	74	64.5	—20	....	...	....	....	..	....	Following subtotal thyroidectomy
Miss F. W.	5530	15	157	+14	120	44.8	— 1	84	47.5	—15	....	...	....	....	..	....	No other treatment
				+17	104	45.8	+ 7	97	47.7	—10							
Mr. E. D.	5663	49	160	+26	80	56.3	—16	70	63.5	—42	....	...	....	....	..	....	No other treatment
Mr. I. C.	5667	41	167	+51	108	70.9	+46	102	70.8	— 5	....	...	....	....	..	....	Preceding operation
				+19	87	68.1	+30	86	74.3	+11	....	...	....	....	..	....	Following subtotal thyroidectomy
Mr. E. S.	6251	35	164	+50	100	55.5	+15	78	53.6	—35	....	...	....	....	..	....	Preceding operation
Mr. A. B.	6312	35	171	+29	101	52.3	+28	100	56.9	— 1	+35	105	58.7	+ 7	2	+ 6	Preceding operation
Mrs. E. R.	6414	34	161	+42	82	52.4	+19	68	53.5	—23	....	...	....	....	..	....	Preceding operation
Average	All observations (28)....			+32			+11			—21							
	All receiving large doses (15).....			+30			+ 8			—22	+ 8			0		—22	
	All in whom basal metabolic rate dropped 10 points or more (23)...			+33			+ 7			—26							
	All in whom basal metabolic rate dropped 10 points or more and who received large doses (13).....			+31			+ 6			—25	+ 6			0		—25	

the small dose with that of the large dose is perhaps not entirely reliable, as the large dose may have been given for too short a time to produce its maximum effect.

For all seventeen patients, the average level of basal metabolism just after admission to the hospital was plus 60 per cent; after a period of rest, it was plus 46 per cent, and after 1 drop of compound solution of iodine daily had had its maximum effect, it was plus 19 per cent. The corresponding figures for the fourteen cases in which observations were also made on larger doses given immediately afterward, were plus 62, plus 48 and plus 19 per cent; and the average basal metabolism on larger doses was plus 21 per cent (table 1).

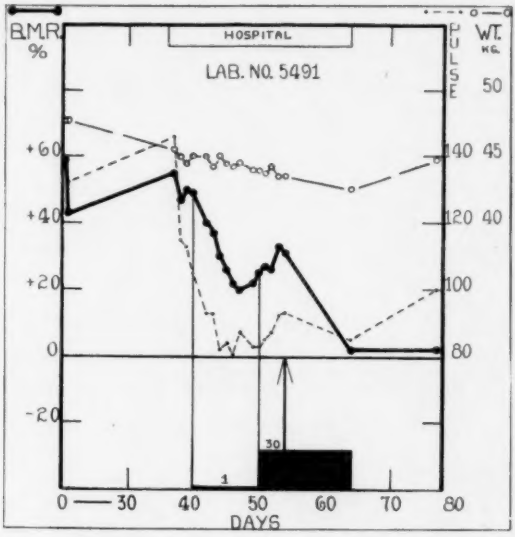

Chart 3.—Well marked reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily, with no further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

From table 3 it may be seen that in twenty-three of twenty-eight observations (82 per cent) on the effect of administering 1 drop of compound solution of iodine daily to twenty-three outpatients, a reduction in basal metabolism of more than 10 per cent was noted. The average level of basal metabolism was plus 32 per cent before iodine was started and plus 11 per cent after 1 drop daily had had its maximum effect. In fifteen observations in which the effect of larger doses (2 to 45 drops daily) given immediately after the small dose was noted, the corresponding figures were plus 30 and plus 8 per cent, and the average

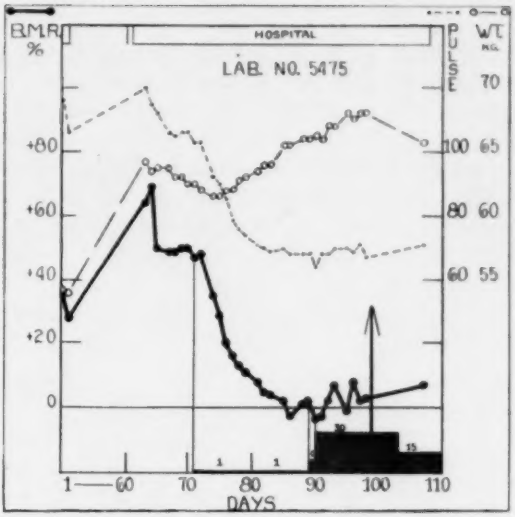

Chart 4.—Marked reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily, with no further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

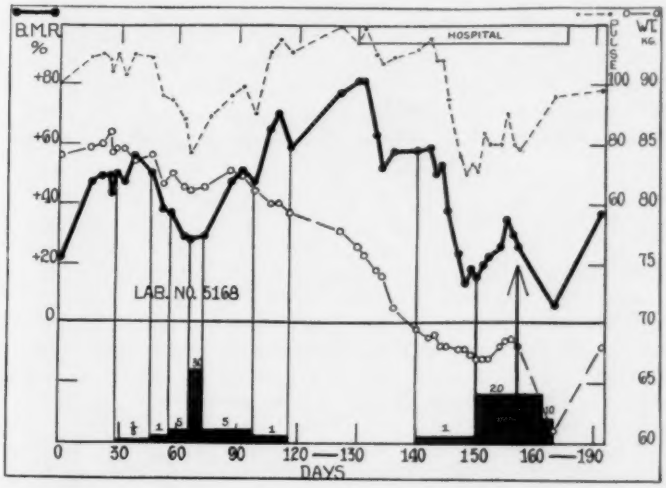

Chart 5.—The effect of slowly increasing and decreasing the dose of iodine. Note that the patient became partially refractory to 1 drop of compound solution of iodine daily while in the outpatient department but that after a short period of omission of iodine she showed a marked reduction in basal metabolism on this dose while in the hospital.

basal metabolism after the larger doses had produced their effect was plus 8 per cent. In three of these observations (20 per cent) the basal metabolism was slightly lower (9 to 12 points) during the administration of larger doses than during the administration of 1 drop daily.

Data on typical individual house cases are recorded in charts 1 to 5, and on an individual outpatient in chart 6.

Starr, Segall and Means,[17] in 1924, reported that the effect on basal metabolism of the administration of 15 drops of compound solution of iodine daily in exophthalmic goiter, was as great in 48 per cent of their series (eight cases) as the immediate effect of removal of five sixths of the thyroid gland in ten cases studied by Segall and Means [18]

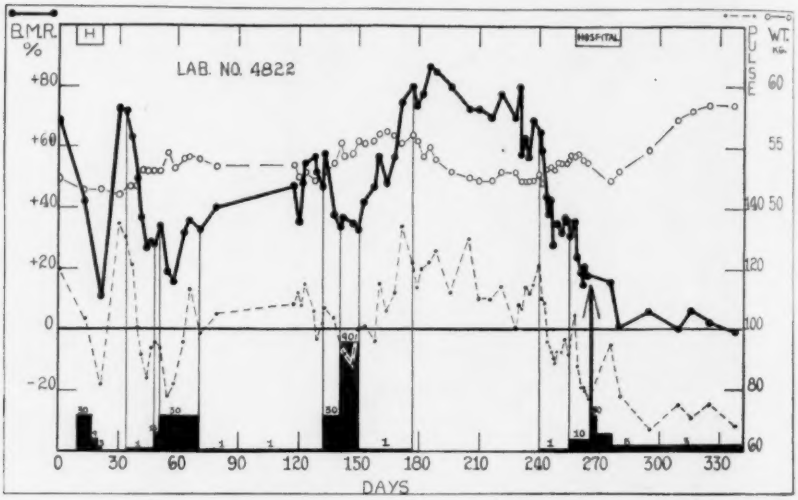

Chart 6.—Well marked reduction in basal metabolism on two occasions (second and third administrations of iodine) in an outpatient during the administration of 1 drop of compound solution of iodine daily. While the patient was slowly becoming completely refractory to 1 drop daily, the temporary administration of from 30 to 90 drops daily depressed the basal metabolism about 20 points below the level at which the small dose held it. Note that although the patient had become completely refractory to 1 drop a day, there was a marked reduction on this dose following a two months' period of freedom from iodine.

17. Starr, P.; Segall, H. N., and Means, J. H.: The Effect of Iodin in Exophthalmic Goiter, Arch. Int. Med. **34**:355 (Sept.) 1924.

18. Segall, H. N., and Means, J. H.: The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter: Daily Basal Metabolism and Pulse Observations, Arch. Surg. **8**:176 (Jan.) 1924.

before the days of iodine. Composite curves of basal metabolism for both their groups of patients are reproduced in chart 8 and compared with a composite curve [19] of basal metabolism (chart 7) for the ten of our seventeen hospital patients (59 per cent) who showed the greatest reduction in basal metabolism during the administration of 1 drop daily. The three curves practically coincide. This is evidence that the reduction in basal metabolism during the administration of 1 drop daily is as great as that during the administration of larger doses.

A GREATER REDUCTION IN BASAL METABOLISM ON LARGER DOSES

It is just as important to study the patients who required more than 1 drop daily to produce a maximum effect, as to study those who did not. Data on such cases are recorded in charts 5, 6, 9 and 10. The data in chart 9 are those of the hospital patient who showed a greater reduction on 30 drops daily than on 1 drop daily.

One of the most significant observations is perhaps the fact that the dose that will produce a maximum effect may vary in the same patient from time to time, evidently on account of a spontaneous variation in the disease. Owing to the same cause, apparently, the response to the same dose may vary in the same patient from time to time. This is shown in chart 10.[20] During the first administration of iodine, little reduction in basal metabolism was observed on 5 drops of compound solution of iodine daily. During the second administration, 1 drop daily had a marked effect, but the subsequent administration of 30 drops daily depressed the metabolism a little more. During the third administration, 1/5 drop daily was given first. It produced a moderate effect, and no further drop occurred on from 1 to 5 drops daily. Nevertheless, the response was less than during the second administration of iodine.

In charts 5 and 6 are presented data on a patient who became partially refractory and on one who became completely refractory, respectively, to a dose o 1 drop of compound solution of iodine daily during the continuous administration of iodine. After iodine was

19. This composite curve was obtained as follows: Working backward and forward from the point at which iodine was begun, we averaged the daily metabolisms of all patients. Where observations on any one patient at rest in bed or on 1 drop daily ended, each curve was stopped. The composite curve therefore, does not show adequately the reduction with rest in bed. In any patient in whom no determination of metabolism was made for one day, the level on this day was supposed to be at the point where the line connecting the determinations on either side crossed it.

20. The data on this case are being published in detail elsewhere (Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Temporary Myxedema During the Administration of Iodine in Exophthalmic Goiter, Am. J. M. Sc., in press) to illustrate another point.

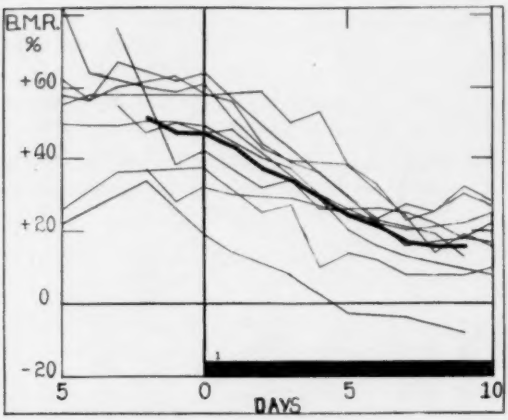

Chart 7.—Composite curve (heavy black line) showing the average rate of reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily in the ten of our cases (nos. 4909, 4949, 4958, 5168, 5272, 5419, 5475, 5491, 5602 and 5656) that showed the greatest response on this dose. The light black lines denote the course of the basal metabolism in individual cases. Cases 5581 and 5596, although showing slightly greater reduction in metabolism than two of the cases included, were omitted because of the infrequency of the observations in case 5581 and their variability in case 5596.

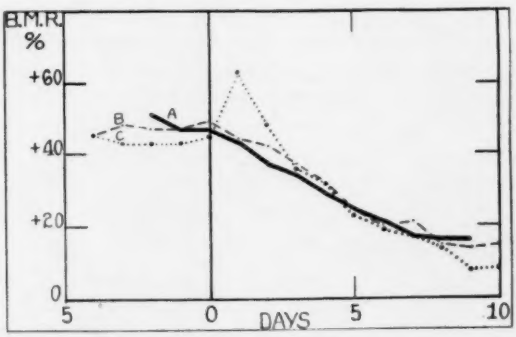

Chart 8.—A comparison of the composite curve of daily basal metabolism for our ten cases which showed the greatest reduction during the administration of 1 drop of compound solution of iodine daily (curve A is taken from chart 7) with that of Starr, Segall and Means for 48 per cent (eight cases) of their series in which 15 drops daily were given (curve B) and that of Segall and Means for ten cases in which the immediate effect of a subtotal thyroidectomy was noted (curve C). The vertical line denotes the point at which treatment was begun. Except for the immediate postoperative rise in C, the three curves practically coincide.

omitted for twenty-four days in the first instance, and for sixty-two days in the second instance, these patients showed a maximum reduction in basal metabolism during the administration of the dose to which they previously had been refractory, viz., 1 drop daily. In the second instance, while the effect of 1 drop of compound solution of iodine a day was slowly wearing off, the temporary administration of from 30 to 90 drops a day caused a reduction in basal metabolism from about plus 55 to about plus 35 per cent. In the first instance,[21] iodine was first given in slowly increasing doses (1/5, 1, 5 and 30 drops daily) and then in slowly decreasing doses (30, 5 and 1 drop daily). There was no response to 1/5 drop and a maximum response on the first admin-

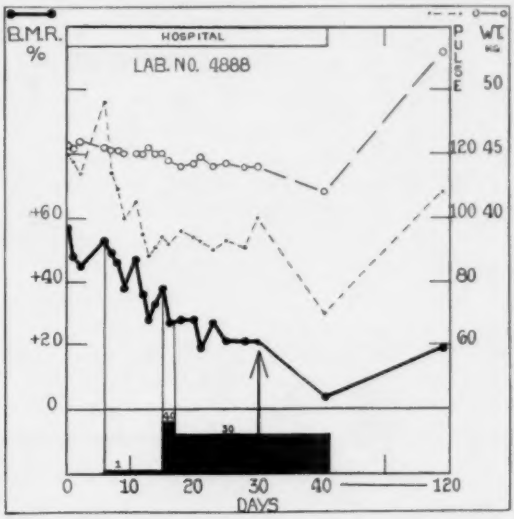

Chart 9.—A moderate reduction in basal metabolism during the daily administration of 1 drop of compound solution of iodine with a slight further reduction during the administration of from 30 to 40 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

istration of 5 drops. As the dose was decreased, the basal metabolism was higher on 5 drops and on 1 drop daily than it had previously been on these doses, and the disease was correspondingly more intense. The data suggest, but by no means prove, that during the period when the metabolism was rising during the administration of iodine, larger doses might have held it at a lower level than did 1 drop daily.

21. Most of the data on this case and some of the data on case 4822 are being published elsewhere (Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Some Experiences with the Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, Arch. Int. Med., in press) to illustrate another point.

These two cases suggest that at stages of the disease in which the patient is becoming refractory to iodine, the effective range of iodine dosage may become placed at increasingly higher levels, until finally no response occurs. Under these circumstances we doubt if the effective dose ever exceeds 5 drops of compound solution of iodine daily. Lack of response to all doses is, of course, sometimes observed in patients who previously received none of this medication.

In cases 3961, 4675 and 4822 (outpatients) the basal metabolism was 9, 12 and 10 points lower, respectively, on larger doses than on 1 drop daily.

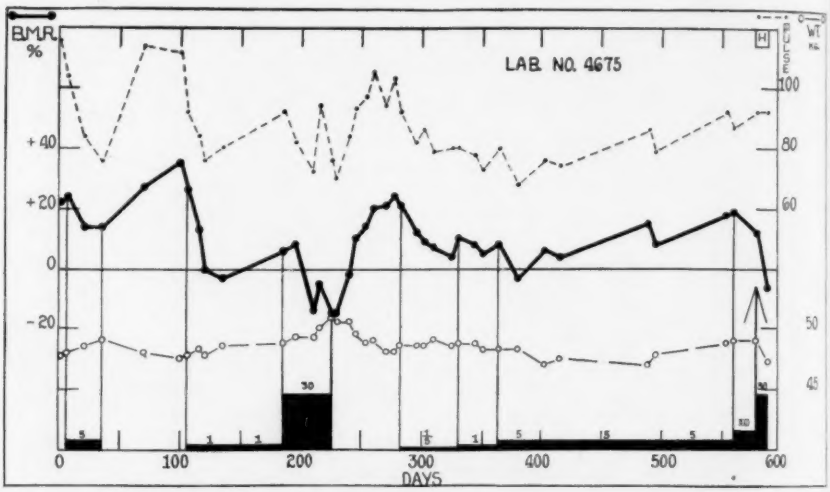

Chart 10.—Variations in the amount of iodine necessary to produce a maximum response, and in the magnitude of the reduction in basal metabolism during the administration of the same dose of iodine at different times to the same patient.

TIME REQUIRED FOR THE REMISSION PRODUCED BY 1 DROP DAILY

It may been seen from chart 8 that the reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily occurred just as quickly as the reduction during the administration of 15 drops daily. This would suggest that the speed of the reduction in basal metabolism is unaffected by the size of the dose so long as it is large enough to produce a maximum effect.

The average time required for the maximum effect to occur in our house patients was seven days. Thus, the average rate of reduction in basal metabolism for house patients who responded was 4.4 points per day. The time varied for the most part between five and eight

days. In one house patient (chart 4) it took fourteen days for the maximum effect to occur; in this patient the rate of decrease became markedly slower as the normal level of basal metabolism was approached.

In our outpatients who received 1 drop daily, observations were usually not made at sufficiently frequent intervals to enable us to determine when the maximum response appeared. In eight cases in which rough calculation was possible, however, it appeared to occur about as quickly as in the house patients.

As one would expect, marked individual variations were noted in the configuration of the curves denoting the drop in basal metabolism. In nine of fourteen cases in which calculation was possible, a drop had started within two days. In five cases it had started within twenty-four hours. A good example of the pronounced influence of this small dose of iodine may be seen in chart 1. In this patient, the dose was forgotten on the second day, yet within forty-eight hours following the administration of only 6 mg. of iodine the metabolic rate had dropped 16 points.

In four cases an interval of three to four days elapsed between the beginning of the administration and the onset of an effect on basal metabolism. This is illustrated well in chart 5. Plummer [22] said that this lag often occurs.

Once the drop had started, it was usually rapid and often appeared to continue at a uniformly rapid rate until a maximum effect occurred, whereupon it stopped abruptly (seven cases). The rapidity of this decrease is not unlike the rapidity with which the basal metabolism drops from the high level produced by the oral administration of desiccated thyroid, on omission of this medication.[23] In three cases a level was reached for two to three days in the curve of descent, following which the basal metabolism appeared to drop as abruptly as previously. In four of the cases, the velocity of the reduction in basal metabolism appeared to decrease as the point of maximum effect was approached.

CONTROL OF REST

The data are recorded in table 1 of this paper, table 1 of the paper on the effect of ½ drop,[24] and table 1 of the paper on the effect of ¼ drop.[16]

22. Plummer, H. S.: Personal communication to the author.

23. Aub, J. C., and Stern, N. C.: The Influence of Large Doses of Thyroid Extract on the Total Metabolism and Heart in a Case of Heart-Block, Arch. Int. Med. **21**:130 (Jan.) 1918.

24. Thompson, W. O.; Thorp, E. G.; Thompson, P. K., and Cohen, A. C.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: II. The Effect on Basal Metabolism of the Daily Administration of Half a Drop of Compound Solution of Iodine, Arch. Int. Med., to be published.

If we had started iodine in our house patients following the initial determination of the basal metabolism and had not secured a resting level, our supposed decrease in this factor in our 1 drop, ½ drop and ¼ drop series would have been about 50, 100 and 200 per cent greater, respectively, than it actually was. Thus it would have appeared that 1 drop reduced the basal metabolic rate 41 points (from plus 60 to plus 19 per cent) instead of 27 points (from plus 46 to plus 19 per cent); that ½ drop reduced it 28 points (from plus 54 to plus 26 per cent) instead of 14 points (from plus 40 to plus 26 per cent); and that ¼ drop reduced it 28 points (from plus 62 to plus 34 per cent) instead of 9 points (from plus 43 to plus 34 per cent). All three doses would thus have appeared to have had a well marked effect on the basal metabolism, and a comparison of their effects would have been hopeless. The importance of securing a resting level of basal metabolism before administering iodine in any study of the effects of different doses or preparations is, therefore, obvious.

A question that naturally arises is whether the resting periods were long enough. As a rule, the basal metabolic rate dropped to a level in from one to six days. The observations of Sturgis [25] and of Kessel, Lieb and Hyman [26] suggest that this level may be maintained for several months. Sturgis noted the effect of rest in bed without other treatment in one patient for 134 consecutive days. The basal metabolism dropped from plus 107 to plus 47 per cent in eleven days and remained at the lower level for 123 more days, at which time operative procedures were begun. The average reduction which Kessel, Lieb and Hyman observed after one month (based on twenty-seven of the first thirty-eight patients reported) was 12 per cent (from plus 44 to plus 32 per cent)—which is roughly the same as Means and Aub [27] and we ourselves noted in from one to three weeks. It thus appears probable that the resting levels we determined would have persisted at least throughout the period covered by iodine medication. It is unfortunate that the data of Kessel, Lieb and Hyman are complicated by the administration of syrup of ferrous iodide after the fourth to the sixth week. It cannot be definitely stated, of course, that in our cases a further reduction would not have occurred from further rest alone. While in forty of the fifty-three patients the

25. Sturgis, C. C.: Observations on One Hundred and Ninety-Two Consecutive Days of the Basal Metabolism Food Intake, Pulse Rate and Body Weight in a Patient with Exophthalmic Goiter, Arch. Int. Med. **32**:50 (July) 1923.

26. Kessel, L.; Lieb, C. C., and Hyman, H. T.: Study of Exophthalmic Goiter and the Involuntary Nervous System: IX. An Estimation of the Pathogenesis and the Evaluation of Therapeutic Procedures in Exophthalmic Goiter, J. A. M. A. **79**:1213 (Oct. 7) 1922.

27. Means, J. H., and Aub, J. C.: A Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism with Remarks Concerning the Effect of Various Forms of Treatment, J. A. M. A. **69**:33 (July 7) 1917.

basal metabolic rate was at a level for more than three days before starting iodine, it was in only a few cases that more than six days elapsed from the time a level was reached until iodine was started. In one case no level was reached; in four the basal metabolism was the same for only two days, and in eight for only three days before starting iodine. In three cases in which the effect of rest (in bed) was noted for twenty, nineteen and eighteen days, the reduction in the basal metabolic rate continued for four, eleven and sixteen days respectively, and in one case in which it was noted for twelve days there was no reduction in metabolism. It would be important to know how much reduction in basal metabolism would have occurred had rest in bed been the only treatment employed for as long a period as that covered by rest and iodine medication in our series. The inconvenience to the patients and the expense of hospitalization for such an investigation are usually not justifiable. Until these data are actually recorded, however, the reduction in basal metabolism caused by any dose of iodine must remain somewhat uncertain.

In case 5168 (chart 5), 1 drop daily was insufficient to produce a maximum response while the patient was at home, but was adequate when she was in the hospital. In view of such data, one wonders whether the minimum dose required to produce a maximum effect sometimes may not be greater under conditions of activity than under conditions of rest. However, the disease may have varied spontaneously; and when the patient was an outpatient, the administration of 1 drop daily was preceded by the administration of 1/5 drop daily, which, as the data on our ¼ drop series[16] suggest, may have interfered with the effect of 1 drop.

COMMENT

From the data presented, it would appear that the minimum amount of iodine that will produce a maximum reduction in basal metabolism in most cases of exophthalmic goiter in Boston is not greater than 6 mg. daily in the form of compound solution of iodine. From the data presented in subsequent papers,[28] it would also appear that it is not much less than 6 mg. daily. The relation of the size of the dose to the storage of colloid is discussed in the paper on the ¼ drop series,[16] in which a general summary of our results to date is given.

Six milligrams of iodine a day is not recommended as a routine in the preparation of patients for operation. In fact, we think it is probably unwise to use a dose that is about adequate to produce a maximum reduction in the basal metabolic rate, but prefer one which supplies a marked excess. There is, moreover, some reason to suppose

28. Thompson, Cohen, Thompson, Thorp and Brailey (footnote 16). Thompson, Thorp, Thompson and Cohen (footnote 24).

that the effect of iodine in exophthalmic goiter cannot be measured entirely by the degree of depression of the basal metabolism.[29] It appears, however, that present doses are needlessly large and unpleasant. In particular, the huge doses (90 minims [5.6 cc.] or more) given in many clinics the day before, the day of and the day after operation are probably of no more value than much smaller doses. It has been satisfactorily demonstrated that iodine does not affect the increase in metabolism following the intravenous injection of thyroxin in rabbits [30] or the administration of thyroid by mouth in man.[31] Iodine therefore presumably acts by producing changes in the thyroid gland. Probably all that it can do postoperatively is to control the thyrotoxicosis in the portion of thyroid gland not removed at operation. Since this portion is usually small, the amount of iodine required for this purpose would also appear to be small. As pointed out above, we doubt if good is ever done by giving more than 5 drops of compound solution of iodine daily. We think this probably would be adequate in the routine preoperative and postoperative treatment of exophthalmic goiter, and see no reason why the dose should be increased at the time of operation.

Several observers [32] are of the opinion that large doses of iodine sometimes may be more detrimental than small doses when the administration is long continued. This opinion is not based on adequately controlled data. In some experiences we have had with the prolonged treatment of exophthalmic goiter by iodine alone,[33] we have seen the condition grow worse after temporary improvement during the continuous administration of small doses (1 drop daily), just as during the continuous administration of large doses (from 15 to 30 drops daily). This has led us to believe that the percentage of cases of exophthalmic goiter which will respond satisfactorily to iodine for an indefinite period is probably little influenced by the size of the dose so long as it is large enough to produce a maximum effect. The problem can be definitely settled, of course, only by giving large doses

29. This opinion is also held by Dr. E. P. Richardson.

30. Sturgis, C. C.; Zubiran, S.; Wells, G. W., and Badger, T.: Effect of Iodine by Mouth on the Reaction to Intravenous Injections of Thyroxin, J. Clin. Investigation **2**:289, 1925.

31. Segall, H. N.: Unpublished data. Carson, D. A., and Dock, W.: The Effect of Iodin upon Experimental Hyperthyroidism in Man, Am. J. M. Sc. **176**: 701, 1928.

32. Cowell and Mellanby (footnote 12). Fraser, F. R.: Iodine in Exophthalmic Goitre, Brit. M. J. **1**:1, 1925. Cole, L. B.: The Use of Lugol's Iodine in Exophthalmic Goitre, Lancet **1**:812, 1927. Marine, D.: Iodin in the Treatment of Diseases of the Thyroid Gland, Medicine **6**:127, 1927. Beebe, S. P.: Iodine in the Treatment of Goiter, M. Rec. **99**:996, 1921.

33. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Some Experiences with the Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, Arch. Int. Med., in press.

of iodine to one group of patients for a long time and small doses to another group for a long time. Large doses have a most unpleasant taste. For this reason alone, when iodine medication is to be long continued, it is desirable to use the smallest dose that will produce a maximum effect (usually 1 drop of compound solution of iodine daily). This applies especially to patients who have residual thyrotoxicosis following a subtotal thyroidectomy for exophthalmic goiter [34] and to a few mild cases of the disease in which treatment with iodine alone may be given.

SUMMARY AND CONCLUSIONS

During the daily administration of 1 drop of compound solution of iodine (about 6 mg. of iodine) to seventeen unselected hospital patients with exophthalmic goiter, fifteen showed a reduction of 15 to 49 points in basal metabolism, and two showed no change. The reduction appeared to be as great as that noted by other observers on much larger doses. A maximum decrease in basal metabolism also appeared to occur in most outpatients during the administration of 1 drop daily.

In the house patients, the administration of 1 drop daily caused a maximum reduction in basal metabolism in seven days on the average.

The time that elapsed between the beginning of iodine administration and the onset of a decrease in basal metabolism varied from one to four days. In five of the cases it had started within twenty-four hours after administering only 6 mg. of iodine.

The doses of iodine used at present in the routine preoperative and postoperative treatment for exophthalmic goiter are probably needlessly large. It is doubtful if more than 5 drops of compound solution of iodine daily is ever necessary to produce a maximum effect.

In comparing the effects of various doses of iodine, it is essential to secure a resting level of basal metabolism before medication is begun.

34. Thompson, W. O.; Morris, A. E., and Thompson, P. K.: Thyrotoxicosis Following Subtotal Thyroidectomy for Exophthalmic Goiter, to be published.

THE DIAZO-COLOR REACTION FOUND IN UREMIA *

I. M. RABINOWITCH, M.D.
MONTREAL, CANADA

In 1925 [1] there was reported a series of results obtained when the blood of patients with various forms of kidney lesions was tested for the diazo-color reaction by Hewitt's modification [2] of Andrewes' original technic.[3] The clinical value of this test was confirmed. Twenty cases in all were observed. It was then found that the reaction was obtained only in cases of severe kidney lesions. In all of the cases in which positive reactions were obtained, the values for blood urea nitrogen were high, ranging between 90 and 210 mg. per hundred cubic centimeters. The creatinine content of the blood specimens was also high. The reaction was not always associated with fatal termination. A patient who had severe nephritis during the course of pregnancy recovered. Nor was there perfect correlation between the degree of retention of urea and the reaction. This was shown in a case of bilateral renal tuberculosis with anuria. The test, then, appeared to be of particular value in differentiating uremia from cerebral arteriosclerosis. As is well known, this differentiation is at times almost impossible to make by the usual clinical methods. The observations may be the same in both conditions; that is, there may be albumin and casts in the urine, hypertension, cardiac hypertrophy, changes in the fundi, headache, muscular twitchings, etc. The best observers often disagree as to whether the signs noted in a given case are due to uremia or to arterial changes in the brain. Since then a number of articles have appeared on the same subject.

Blotner and Fitz [4] obtained positive diazo-color reactions in cases with lesser degrees of nonprotein nitrogen retention in the blood than those previously reported. These authors, again, pointed out the prognostic value of the test. They stated that a high blood urea nitrogen test did not have the same prognostic significance when the diazo-color reaction was negative as when it was positive. They also observed that the test was of value in differentiating uremia from other forms of coma.

---

* Submitted for publication, June 29, 1929.

* From the Department of Metabolism, the Montreal General Hospital.

1. Rabinowitch, I. M.: Canad. M. A. J. **15**:725, 1925.

2. Hewitt, L. F.: Biochem. J. **19**:171, 1925.

3. Andrewes, C. H.: Lancet **1**:590, 1924.

4. Blotner, H., and Fitz, R.: Diazo Test in Nephritis, J. A. M. A. **88**:985 (March 26) 1927.

Almost simultaneously, Harrison and Hewitt [5] and Hunter and Montgomery [6] reported somewhat similar experiences. Harrison and Hewitt made the additional observation that, on boiling the mixture of protein-free filtrate and the diazo-color reagent, though a yellow brown was always found in the positive case, a similar color may also be obtained with substances other than that responsible for the Andrewes' reaction. Hewitt's modification of Andrewes' procedure, that is, the use of the red color obtained on making the mixture alkaline after heating, eliminates this difficulty. The test thus performed was found positive only in persons with severe kidney damage. Other observations made were: (*a*) A negative reaction does not exclude uremia, and (*b*) the degree of urea retention and the diazo-color reaction do not run strictly parallel. The test was somewhat simplified in order to make it of greater clinical application. Hunter and Montgomery also suggested a modification of the test to increase its sensitivity. Both Harrison and Hewitt and Hunter and Montgomery made the observation that the substance responsible for the reaction is a constituent of normal urine. Harrison and Bromfield [7] have shown that the substance responsible for the reaction is an indoxyl compound, presumably indican, or possibly, in part, indoxyl glycuronate.

Since then, a paper has been published by Rabson and Jacobs,[8] reporting their experiences with twenty-one cases. These authors showed that four of seven patients whose blood gave positive diazo-color reactions are now living, and their general condition is improved. It was also observed that the test was not positive in all of the cases of coma associated with severe kidney damage, and that it did not always differentiate uremia from the comas of other origin. The conclusion was also made that the creatinine content of blood is of greater value than the diazo test in estimating the extent of kidney damage.

In the laboratory of this hospital the test has been part of the routine in the study of kidney efficiency, since it was first reported, and many hundreds of observations have been made. Clinical and laboratory records have been carefully recorded and correlated. The purpose of this paper is to report further experiences. These demonstrate that, when certain variables are considered in the interpretation of the data, there is no reason to alter the original view expressed as to the prognostic value of this test. In other words, this test differs in no way from all other laboratory procedures, for the proper use of which it is important to correlate laboratory results with clinical signs and symptoms.

5. Harrison, G. A., and Hewitt, L. F.: Brit. M. J. **2**:1138 (Dec. 17) 1927.

6. Hunter, G., and Montgomery, R. C.: Canad. M. A. J. **17**:1448, 1927.

7. Harrison, G. A., and Bromfield, R. J.: Biochem. J. **22**:43, 1928.

8. Rabson, S. M., and Jacobs, L.: Value of Diazo Test on the Blood, Arch. Int. Med. **42**:386 (Sept.) 1928.

In view of this experience, I have not found any reason for modifying the procedure described by Hewitt, except that instead of boiling the mixture for thirty seconds as described before making the mixture alkaline, it is allowed to remain in water for about five minutes after the water has been brought to the boiling point and the flame removed. It was frequently noted that heating the test tube directly over the flame led to negative results when the substance responsible for the reaction was actually present. That the temperature of the mixture prior to the addition of alkali is an important factor is also suggested from the recent observations of Harrison,[9] who found that if the concentration of the substance responsible for the reaction is very small, it is easy to miss the fleeting red tint if the alkali is added to the hot mixture. To overcome this, the mixture, after it has been boiled sufficiently to produce the maximum brown color, is cooled under the tap. The alkali is then added.

It is recognized, clinically, that persons may have severe lesions of the kidney and recover. These include the albuminurias of severe infections, the well recognized acute nephritis with pallor, edema and other changes, mechanical obstructions to the urinary outflow, some surgical lesions of the kidney, anuria of diabetic coma, and other conditions. The blood of such persons may show marked retentions of urea and creatinine and give positive diazo reactions. In such cases, therefore, the diazo-color test differs in no way from the estimation of the urea and creatinine contents of blood. The importance of considering these forms of acute kidney damage in the interpretation of the urea and creatinine contents of blood was emphasized some time ago.[10]

In our experience, at least, the diazo-color test has proved to be most reliable, from the point of view of prognosis in chronic nephritis. Persons suffering from such acute lesions of the kidney referred to and whose blood may give positive reactions may, just as stated, recover, but we have yet to observe a person with chronic nephritis who has recovered when the lesion of the kidney has progressed to the point of giving a positive reaction. The longest period observed, between the time the positive reaction was first observed and death, was five months.[11] Here, again, must be excluded acute exacerbations which may occur during the disease. The latter should obviously be included among the acute lesions of the kidney. Clinically, it is recognized that persons frequently recover from these acute exacerbations.

9. Harrison, J. A.: Personal communication to the author.

10. Rabinowitch, I. M.: Canad. M. A. J. **11**:320, 1921.

11. One patient has now been under observation for more than one year with a positive reaction, but the diagnosis is uncertain. There appears to be a combination of chronic nephritis and a surgical lesion with pyuria.

When an attempt was made to correlate the positive reactions with the urea contents of blood in our large series of cases, no correlation was noted. This is shown in table 1. The positive reactions only are recorded. This observation was to be expected, since the prognosis and degree of retention of blood urea are not related.

In the many hundreds of analyses that have been made, though high blood urea values were found associated with negative diazo-color

TABLE 1.—*Absence of Relationship Between Blood Urea Nitrogen and Diazo-Color Reaction*

Urea Nitrogen, Mg. per 100 Cc. of Blood	Incidence of Positive Diazo-Color Reaction
-21	0
21-30	26
31-40	11
41-50	8
51-60	24
61-70	12
71-80	14
81-90	18
91-100	8
101-110	6
111-120	9
121-130	8
131-140	22
141-150	10
151-160	21
161-170	18
171-180	12
181-190	10
191-200	6
201-	14

TABLE 2.—*Relationship Between Positive Diazo-Color Reaction and Creatinine Content of Blood*

Creatinine, Mg. per 100 Cc. of Blood	Incidence of Positive Diazo-Color Reaction
-1.50	0
1.51-1.75	0
1.76-2.00	0
2.01-2.25	3
2.26-2.50	5
2.51-2.75	5
2.76-3.00	6
3.01-3.25	8
3.26-3.50	7
3.51-3.75	11
3.76-4.00	14
4.01-4.25	16
4.26-4.50	20
4.51-4.75	15
4.76-5.00	25
5.01-	41

reactions, we have yet to find a positive diazo-color reaction associated with a normal blood urea nitrogen. Rabson and Jacobs reported such a case (subject S. F.).

The observations with regard to the relationship between positive reactions and the creatinine content of blood differ from those with regard to urea. Here there appears to be a relationship. The results are shown in table 2. Only positive reactions are, again, recorded.

Here, again, our observations differ from those of Rabson and Jacobs. We have yet to observe a positive diazo-color reaction with a creatinine value of less than 2 mg. per hundred cubic centimeters of blood. With regard to negative reactions, Rabson and Jacobs, in a series of fourteen cases, found four patients whose blood gave such reactions, in spite of creatinine values greater than 5 mg. per hundred cubic centimeters. In our series, only two of forty-three specimens of blood with such creatinine values were met with which gave negative diazo-color reactions.

When consideration is given to the different forms of kidney lesions and to the view previously reported regarding the urea-creatinine relationships,[12] an explanation for the aforementioned observations is suggested. In both of our cases with creatinine values greater than 5 mg. per hundred cubic centimeters of blood and negative diazo-color reactions, the anurias were due to mechanical block (prostatic hypertrophy). Of the four patients in the cases reported by Rabson and Jacobs whose blood gave positive diazo-color reactions and who recovered, three had acute lesions. G. R. had acute suppression of urine following parturition, H. M. had prostatic hypertrophy with urinary retention, and J. C. had urinary retention with acute cholecystitis.

CONCLUSIONS

Our experiences with the diazo-color reaction, therefore, lead to the following conclusions:

1. A positive diazo-color reaction is not found in any condition other than severe kidney damage.

2. A positive reaction may frequently be found in persons with severe kidney damage, and such persons may recover. Such cases include the albuminurias of severe infections, the well recognized form of acute nephritis with pallor, edema, etc., acute exacerbations of chronic nephritis, mechanical obstructions to the urinary outflow, surgical lesion of the kidneys with urinary retention and the anuria of diabetic coma.

3. When acute exacerbations of the disease are excluded, a positive reaction occurring in the course of chronic nephritis has invariably, at least in our experience, meant unfavorable prognosis.

4. When all of the aforementioned factors are given consideration, the test is of value in differentiating uremia from cerebral arteriosclerosis.

---

12. Patch, F. S., and Rabinowitch, I. M.: Urea and Creatinine Contents of Blood in Renal Disease: Statistical Analysis of 5,000 Observations, J. A. M. A. **90**:1092 (April 7) 1928.

BLOOD OF NORMAL YOUNG WOMEN RESIDING IN A SUBTROPICAL CLIMATE

RED CELLS, HEMOGLOBIN, VOLUME OF PACKED RED CELLS, COLOR INDEX, VOLUME INDEX AND SATURATION INDEX *

M. M. WINTROBE, M.D., PH.D.
NEW ORLEANS

An investigation similar to that previously reported in 100 young men residing in the Southern United States [1] has been carried out on 50 women between the ages of 17 and 30 residing in the same region. This work was undertaken, in the first place, to determine the validity of the hypothesis that an anemia of purely climatic origin is present in otherwise healthy persons residing in tropical and subtropical climates and is the cause of the pallid appearance of many of these persons, and, secondly, in order to furnish further data from which to calculate normal blood standards. In spite of the fundamental importance of accurate knowledge in respect to the number of red cells, the amount of hemoglobin and the volume of packed red cells in the blood of normal healthy persons, it is surprising to find on what poor foundation the accepted standards have been based.

The usually accepted conceptions of the normal blood count in men and women are founded on determinations made in the middle of the nineteenth century on four subjects by Vierordt [2] and Welcker.[3] Since that time the few investigations which have been undertaken have not advanced the knowledge in this field in any manner commensurate with the progress in other fields of medicine. In spite of the common knowledge of the degree of error entailed in the counting of red cells, as well as the wide variation observed in healthy persons, it was only recently that the validity of drawing conclusions on the basis of only a few

* Submitted for publication, July 10, 1929.

* From the Department of Medicine, Tulane University School of Medicine.

1. Wintrobe, M. M., and Miller, M. W.: Normal Blood Determinations in the South, Arch. Int. Med. **43**:96 (Jan.) 1929. Wintrobe, M. M.: Hemoglobin Standards in Normal Men, Proc. Soc. Exper. Biol. & Med. **26**:848 (June) 1929.

2. Vierordt, K.: Zählungen der Blutkörperchen des Menschen, Arch. f. Physiol. **11**:*327*, 1852.

3. Welcker, H.: Des Gehalt des Blutes in gefärbte Körperchen, approximativ bestimmt nach bei der methodischer Verdunnung des Blutes ensthenden Färbung. Arch. d. Ver. f. gemunsch. Arb. z. Ford. d. wissench. Heilkund., Göttingen **1**:195, 1854.

observations was questioned and an attempt was made to supply a large series of observations in healthy men [4] and women.[5]

Likewise, the wide variation in the amount of hemoglobin accepted as the equivalent of 100 per cent by the various hemoglobinometers reflects the inaccurate foundation on which they are based. Finally, the value of information derived from a knowledge of the volume of packed red cells in a given sample of blood, which can be determined more easily and, incidentally, more accurately than either the number of red cells or the amount of hemoglobin, has received little attention and its importance in clinical diagnosis has been practically neglected.

SUBJECTS EXAMINED

The subjects of this examination were normal female students between the ages of 17 and 30. Twelve were medical students and the remainder, students in the general academic courses of Newcomb College. The majority had had a physical examination in the past year, and all felt well at the time of the examination. Many habitually took part in athletics. Practically the entire group was born in the United States, the majority of American-born parents. All have resided in the Southern States (chiefly Louisiana, Mississippi and Alabama) for at least the last three years. The examinations were made during the months of February, March and April, during which time the atmospheric temperature ranged between 50 and 84 F.

No selection was made with reference to the menstrual period. The examinations were conducted whenever the subjects chose to present themselves, whether they were menstruating at the time or not. The time in the menstrual cycle at which the examinations were made, however, was noted. The possible influence of menstruation will be discussed elsewhere.

Most of the specimens of blood were drawn after noon, between 1 and 5 p. m., while a few were drawn earlier in the day.

METHODS

Five cubic centimeters of venous blood was drawn from a vein of the arm into a dry syringe and quickly placed in test tubes containing 10 mg. of finely powdered neutral potassium oxalate with which the blood was thoroughly mixed. Care was taken to keep the tourniquet on the arm for as brief a time as possible in order to avoid any error introduced by congestion of the arm.

---

4. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards, Arch. Int. Med. **37**:685 (May) 1926.

5. Osgood, E. E., and Haskins, H. D.: Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, Arch. Int. Med. **39**:643 (May) 1927.

The method of using venous blood for determining red cell counts and hemoglobin instead of capillary blood, as is the custom, requires some consideration. The use of venous blood has the merit that, in normal persons at least, flow in the veins is always active and determinations are more likely to be constant, whereas the influence of stasis, cold and other temporary external factors may be encountered in the capillaries.[6] Furthermore, unless a free flow of blood is obtained by means of a deep wound, serum and lymph may be squeezed out from the finger or ear instead of a truly representative quantity of red cells. My own investigations show that there is no regular difference between cell counts and hemoglobin determinations made on blood taken from the vein or the finger pulp. The experience of others supports this conclusion.[7]

The addition of oxalate to venous blood in the proportion of 10 mg. to 5 cc. of blood has no influence on red cell count or hemoglobin, although a shrinkage of 3.7 per cent in cell volume is produced.[1]

The technic followed in the determination of red cell counts and hemoglobin was the same as in the earlier work on men [1] and need not be again described. For the determination of cell volume a specially made hematocrit was used. This hematocrit is described in detail elsewhere.[8] It was substituted for the specially calibrated centrifuge tube used in the work on men because less blood is required, and the reading of cell volume is more easily and more accurately made. Complete packing was secured by centrifugation at 3,000 revolutions per minute for thirty minutes. As the heat produced in the centrifuge caused a slight expansion of the blood, readings were not made until the tubes had regained the temperature of the surrounding air. An addition of

6. Drinker, C. K.: The Pathological Physiology of Blood Cell Formation and Blood Cell Destruction, Oxford Medicine, vol. 2, pt. 2, p. 509.

7. Yarbrough, N.: Blood Counts with Oxalated Blood, J. Lab. & Clin. Med. **7**:172 (Dec.) 1921. Foord, A. G.: Blood Counts with Oxalated Blood Compared with Ordinary Counts, J. Lab. & Clin. Med. **8**:343 (Feb.) 1923. DaCosta, J. C.: Clinical Hematology, Philadelphia, P. Blakiston's Son & Company, 1907, p. 173. Bürker, K.: Vergleichende Untersuchungen über den Gehalt des menschlichen Blutes an Hämoglobin und Erythrocyten in verschiedenen Teilen des Gefäss-systems, Arch. f. d. ges. Physiol. **167**:143 (April) 1917. Bing, H. I.: On the Number of Red Blood Corpuscles at Different Ages and Under Different Circumstances, Acta med. Scandinav. **53**:833, 1921. Hess, Otto: Vergleichende Untersuchungen am arteriellen, kapillaren und venösen Blut des Menschen, Deutsches Arch. f. klin. Med. **137**:200 (Aug.) 1921. Duke, W. W., and Stofer, D. D.: A Comparison of Capillary and Venous Blood in Pernicious Anemia, Arch. Int. Med. **30**:94 (July) 1922. Rud, E. J.: Le nombre des globules rouge chez les sujets normaux et leurs variations dans les diverses conditions physiologiques, Acta med. Scandinav. **57**:142, 1922-1923. Osgood (footnote 4).

8. Wintrobe, M. M.: A Simple and Accurate Hematocrit, J. Lab. & Clin. Med. **15**:287 (Dec.) 1929.

3.7 per cent was made to the cell volume determined in each case in order to allow for shrinkage resulting from the addition of oxalate to blood in the proportions mentioned.

ACCURACY OF METHODS EMPLOYED

Red Cell Counts.—As in the earlier work,[1] two separate dilutions of blood were made and the resulting counts were not accepted unless they agreed within 100,000, the average of two such counts being taken as the result. Calculation of the probable error [9] shows that this method involves an error of less than 1 per cent. However, since it is possible that two closely agreeing counts may be accidental and that two subsequent counts would differ from these first ones, although again agreeing between themselves, the probable error is more accurately determined

TABLE 1.—*Consecutive Counts on a Single Specimen*

Count No.	No. of Cells Counted	d or Variation from Mean	d^2
1	518	+11	121
2	520	+13	169
3	502	− 5	25
4	505	− 2	4
5	491	−16	256
Mean	507		Σ 575

The probable error is $0.67449\sqrt{\frac{575}{5}} = 7.23$

The percentage of error in terms of the mean is $\frac{7.23}{507} \times 100 = 1.43$ per cent

by calculation on the basis of the results of several consecutive counts on a single sample of blood. In the example given in table 1 five different dilutions and counts were made.

From these and other similar calculations it is concluded that the probable error of the red-cell counts carried out by the method described is not greater than 2 per cent.

Hemoglobin.—The amount of hemoglobin was determined by means of a Newcomer hemoglobinometer restandardized on the basis of a series of parallel determinations by the van Slyke method.[1] In considering the probable error of the hemoglobin determinations, it is necessary to consider the error entailed in the actual reading of the Newcomer instrument as well as the probable error of the correction curve. The result of such an analysis is rather disconcerting. While the probable

9. Probable error can be determined from the standard deviation of a series of consecutive determinations on the same sample of blood. The standard deviation (δ) is calculated from the formula $\delta = \sqrt{\frac{\Sigma\,(d^2)}{N}}$, where $\Sigma\,(d)^2$ is the sum of the squares of the differences of the individual readings from the mean of those readings, and N is the number of readings. The probable error is 0.6745δ.

error of the actual reading of the Newcomer instrument is less than 2 per cent and that the van Slyke determinations approximately 1 per cent, the twenty-nine determinations, on which the correction for the hemoglobinometer used is based, showed a rather high degree of scatter about the correction curve. Thus, samples of blood which gave approximately the same readings on the Newcomer instrument showed an appreciable difference in oxygen capacity and corresponding hemoglobin equivalent as determined by the van Slyke method. The probable error of the correction curve, as calculated by measuring the difference between the actual van Slyke determination for each sample of blood and its equivalent on the theoretical correction curve, is 9.2 per cent.

On the basis of these calculations, then, the total possible error of the hemoglobin determinations reported is from 10 to 12 per cent. In these calculations the error has been exaggerated rather than minimized, and it is likely that the actual error is not so great. I feel that the results here reported are certainly comparable in accuracy with the figures reported by others. It is important to realize, however, that even after careful recalibration of one of the more accurate hemoglobinometers, a rather considerable degree of error may be present. The error resulting from the placid acceptance of the manufacturer's statement that 100 per cent is equivalent to a certain number of grams of hemoglobin is, however, much greater. Thus, in the case of the particular Newcomer instrument which I have attempted to recalibrate, a sample of blood reading 70 per cent showed an oxygen capacity (van Slyke) equivalent to 14.61 Gm. The equivalent of 70 per cent by the correction curve developed is 14.1 Gm., while its equivalent on the manufacturer's statement that 100 per cent on the Newcomer hemoglobinometer is equivalent to 16.9 Gm. would be 11.83 Gm.

It is worth noting that the Newcomer method of hemoglobin determination is much more accurate than the methods more commonly used in clinical medicine. The error of these latter methods is from 20 to 30 per cent or even greater. The only redeeming feature of the commonly used methods of hemoglobin determination is that, although they are almost worthless for the determination of the absolute amount of hemoglobin in the blood, some instruments afford moderately accurate relative conceptions.

Cell Volume.—Two hematocrit determinations were made on each specimen of blood and the average of these two was recorded. With reasonable care in technic the determination of cell volume by the hematocrit method is very accurate. Samples frequently check exactly. The example in table 2 has been chosen to illustrate the determination of the probable error because it represents greater rather than less than usual variation.

The actual variation between several samples of the same specimen of blood is thus no greater than 0.5 per cent. It is surprising that a method which is so simple and yet so accurate has received so little use in clinical laboratory diagnosis. This is explained chiefly by the fact that the value of the information which can be derived from the hematocrit has received little emphasis.

THE RED CELL COUNT IN NORMAL WOMEN

Red cell counts made with reasonable accuracy have been reported for 126 women between the ages of 17 and 30:

Bierring[10] (Sweden) ..... 3 women, averaging 4.24 million
Gram and Norgaard[11] (Denmark) ..... 6 women, averaging 4.59 million
Bie and Möller[12] (Denmark) ..... 10 women, averaging 4.74 million
Rud[13] (Denmark) ..... 8 women, averaging 4.80 million
Haden[14] (Missouri) ..... 9 women, averaging 4.33 million
Osgood and Haskins[5] (Oregon) .....100 women, averaging 4.80 million

Total, 136 women, averaging 4.74 million per cubic millimeter.

TABLE 2.—*Consecutive Hematocrit Determinations on a Single Specimen*

Sample No.	Reading, Cc.	d	d^2
1	37.1	−0.3	0.09
2	37.3	−0.1	0.01
3	37.6	+0.2	0.04
4	37.4	0	0
5	37.8	+0.4	0.16
6	37.5	+0.1	0.01
Mean	37.4		0.31

$$\delta = \sqrt{\frac{0.31}{6}} = 0.2273$$

P. E. $\delta = 0.67449 \times 0.2273 = 0.1533$

Probable error in per cent of mean $\frac{0.1533}{37.4} \times 100 = 0.41$ per cent

Osgood and Haskins[5] quoted 184 counts made by ten different investigators on women whose age is not given. The average of these counts is 4.83 million.

The average of counts in the fifty normal women examined in New Orleans is 4.93 million. Unlike the counts in men in the South,[1] there

10. Bierring, K.: Svingninger i erythrocyttallet hos normale mennesker, Ugesk. f. Laeger **82**:1445 (Nov.) 18 1920; quoted by Osgood and Haskins (footnote 5).

11. Gram, H. C., and Norgaard, A.: Relation Between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects, Arch. Int. Med. **31**:164 (Feb.) 1923.

12. Bie, Valdemar; and Möller, Paul: Constitution du sang humain normal, Arch. d. mal. du coeur **15**:177 (April) 1922.

13. Rud (footnote 7, eighth reference).

14. Haden, R. L.: Accurate Criteria for Differentiating Anemias, Arch. Int. Med. **31**:765 (May) 1923.

is no significant difference between the results of counts made in this locality and those made elsewhere. The average of erthrocyte counts made on 186 women, from 17 to 30 years of age, in different parts of the world is 4.78 million.

Chart 1 is a histogram showing the frequency distribution of red cell counts in the fifty normal women. The mean (4.93 ± 0.03) and the median (4.94 ± 0.03) are practically equal and both coincide with the peak of the curve. The tendency to a double peak is not significant. The standard deviation is 0.286 ± 0.018 million, and the coefficient of variation 5.8 per cent.[15] Thus the significant variation of the red cell counts was between 5.22 and 4.64 million (actually 76 per cent ranged

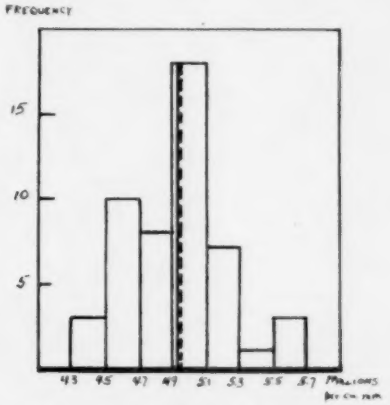

Chart 1.—Histogram showing frequency distribution of variations in red cell counts in fifty young women. The mean is indicated by a straight line, the median by an interrupted line.

between these figures). These results correspond closely to the counts reported by Osgood and Haskins excepting that the latter authors found a larger proportion of counts below 4.5 million.

15. The methods of analyzing the observations here reported are those recommended by Raymond Pearl (Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1927, p. 264), and the manner of calculating the various constants is that recommended by this author. The central tendency in a group of observations is measured by the usual arithmetical mean or average, and also by the median. The latter is simply the middle value in a series of observations, 50 per cent of the variates falling above and 50 per cent below it. In a large series of observations, if the distribution of cases is symmetrical, the median will approach closely to the average. The degree of variation is measured by means of the standard deviation and the coefficient of variation. The standard deviation is a constant which has been adopted by biometricians to measure in absolute terms

TABLE 3.—*Observations on the Blood of Fifty Normal Young Women*

Subject	Age	Red Cell Count, Millions per C.Mm.	Hemoglobin, Gm. per 100 Cc.	Hemoglobin, Gm. per 100 Cc. per 5 Million Cells	Color Index	Volume of Cells Cc. per 100 Cc.	Volume of Cells per 100 Cc. per 5 Million Cells	Volume Index	Saturation Index
1	22	5.54	14.95	13.50	0.95	39.3	35.6	0.83	1.15
2	28	4.69	12.88	13.72	0.96	37.9	40.5	0.95	1.01
3	18	5.08	13.90	13.69	0.96	38.9	38.3	0.90	1.08
4	20	5.65	15.75	13.95	0.98	41.9	40.6	0.87	1.03
5	17	4.99	14.95	14.99	1.05	38.7	38.8	0.91	1.16
6	21	5.04	13.39	13.20	0.93	38.6	38.3	0.90	1.04
7	18	5.04	15.32	15.21	1.07	39.3	39.0	0.91	1.18
8	24	5.15	14.95	14.51	1.02	42.7	41.4	0.99	1.05
9	20	5.59	15.12	13.52	0.95	41.2	36.9	0.87	1.10
10	20	5.23	14.10	13.49	0.95	39.3	37.6	0.88	1.08
11	19	4.95	14.20	14.39	1.01	41.7	42.1	0.98	1.02
12	20	4.86	13.10	13.49	0.95	37.2	38.3	0.90	1.06
13	19	4.89	13.10	13.40	0.94	36.8	37.6	0.88	1.07
14	20	5.15	13.30	12.90	0.91	40.9	39.7	0.93	0.98
15	19	5.00	13.30	13.30	0.94	36.9	36.9	0.86	1.09
16	20	4.59	12.66	13.57	0.97	39.3	42.8	1.00	0.97
17	20	5.05	14.53	14.40	1.01	41.2	40.8	0.96	1.12
18	20	5.06	13.80	13.13	0.96	40.5	40.0	0.93	0.99
19	18	4.56	12.46	13.89	0.96	37.1	40.7	0.95	1.02
20	23	5.26	15.96	15.18	1.07	43.6	43.0	0.97	1.10
21	20	5.07	14.20	14.00	0.99	41.6	41.0	0.96	1.03
22	21	5.13	14.10	13.74	0.97	39.9	38.9	0.91	1.06
23	18	4.55	11.80	12.98	0.91	36.3	39.9	0.93	0.98
24	19	4.90	13.50	13.79	0.97	40.9	41.8	0.96	1.01
25	19	4.90	12.46	12.70	0.90	40.4	41.2	0.96	0.93
26	21	4.89	13.30	13.60	0.96	40.0	40.9	0.95	1.00
27	20	4.68	13.20	14.10	0.99	37.5	40.1	0.94	1.06
28	22	4.81	14.30	14.88	1.04	38.5	40.0	0.94	1.12
29	23	4.66	13.70	14.70	1.03	38.9	41.7	0.98	1.06
30	22	4.67	13.90	14.89	1.05	39.2	42.0	0.98	1.07
31	21	4.47	12.46	13.91	0.98	36.0	40.2	0.94	0.98
32	21	4.74	14.10	14.90	1.05	39.0	41.2	0.96	1.09
33	20	5.10	14.74	14.94	1.02	41.2	40.4	0.89	1.08
34	22	4.52	12.90	14.38	1.01	35.7	39.5	0.92	1.10
35	30	4.79	13.50	14.10	0.99	38.1	39.8	0.93	1.07
36	18	4.64	12.88	13.88	0.98	38.0	42.0	0.91	1.02
37	17	4.47	12.46	13.91	0.98	36.6	40.9	0.91	1.04
38	25	5.65	12.88	12.71	0.90	39.9	39.5	0.92	0.97
39	28	4.97	14.10	14.19	1.00	38.4	38.6	0.90	1.10
40	22	5.10	15.75	15.45	1.09	42.4	41.5	0.97	1.12
41	31	4.96	14.10	14.20	1.00	40.5	40.8	0.95	1.05
42	19	4.94	13.50	13.69	0.96	41.9	42.4	0.99	0.97
43	31	4.65	13.50	14.50	1.02	39.2	42.4	0.99	1.04
44	20	4.94	13.70	13.99	0.98	40.2	40.7	0.90	1.08
45	19	5.48	15.12	13.80	0.97	44.3	40.4	0.95	1.03
46	20	5.01	14.41	14.39	1.01	42.6	42.5	0.99	1.02
47	19	4.84	14.00	14.48	1.02	40.1	41.5	0.97	1.05
48	23	5.07	11.80	11.62	0.82	35.8	35.2	0.82	0.99
49	24	4.45	13.10	14.71	1.04	37.7	42.3	0.99	1.05
50	27	4.87	13.50	13.84	0.98	38.5	39.5	0.93	1.06
Averages		4.93	13.76	13.97	0.98	39.5	40.3	0.93	1.05

(millions, grams, etc.) the degree of scatter or dispersion of a group of observations. It is a much more accurate index of variation than are maximum and minimum values since the latter are often manifestations of abnormalities or the result of technical error. The coefficient of variation expresses the standard deviation as a percentage of the mean and is thus an expression of the relative dispersion of the variates. The coefficient of variation makes possible the comparison of the variability of any series of observations. Thus in the series here examined the coefficient of variation for red cell counts was 5.8 per cent while that for hemoglobin was 7.2 per cent.

HEMOGLOBIN CONTENT OF THE BLOOD OF NORMAL WOMEN

Hemoglobin determinations made by relatively reliable methods are available for 172 normal women between the ages of 17 and 30. They are as follows:

Williamson[16] (spectrophotometer) ..... 49 women, averaging 15.11 Gm.
Bie and Möller[32] (Meisling colorimeter checked by oxygen method) ..... 10 women, averaging 13.30 Gm.
Gram and Norgaard[33] (Autenreith Königsberger colorimeter checked by oxygen method)..... 6 women, averaging 12.82 Gm.
Rud[33] (Autenreith-Königsberger checked by oxygen method) ..... 8 women, averaging 12.28 Gm.
Haden[34] (van Slyke's method) ..... 9 women, averaging 13.50 Gm.
Osgood and Haskins[5] (Osgood-Haskins method) .....100 women, averaging 13.69 Gm.
Total, 182 women, averaging 13.95 gm. per hundred cubic centimeters of blood.

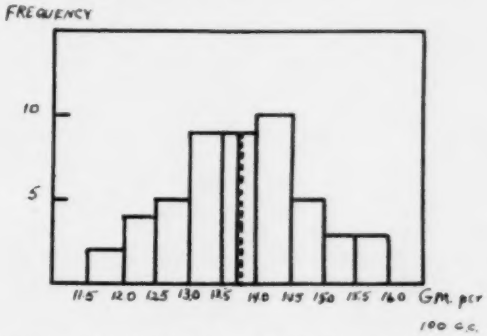

Chart 2.—Histogram showing frequency distribution of variation in hemoglobin in fifty young women.

Osgood and Haskins quoted additional determinations on 133 women whose ages are not given, or in which the methods used were of doubtful accuracy. The average of these is 12.99 Gm.

The average of 13.76 Gm. in the fifty women examined in New Orleans is only slightly lower than the general average and like the red cell counts is not significantly different from observations in other parts of the world. The average of the 232 hemoglobin determinations made on women between the ages of 17 and 30 is 13.91 Gm.

Chart 2 is a histogram showing the frequency distribution of hemoglobin determinations in the fifty women examined. The mean (13.76 ± 0.09) and the median (13.77 ± 0.12) practically coincide. The standard deviation of this series is 0.99 ± 0.07 Gm., and the coefficient of variation 7.2 per cent. The significant variation was thus

16. Williamson, C. S.: Influence of Age and Sex on Hemoglobin, Arch. Int. Med. **18**:505 (Oct.) 1916.

between 12.77 and 14.75 Gm. (Actually 68 per cent ranged between these figures.) This corresponds to Osgood and Haskins' results.

HEMOGLOBIN COEFFICIENT AND COLOR INDEX

The importance of the determination of an accurate standard to serve as the equivalent of 100 per cent hemoglobin has been recently emphazied.[17] Without an accurate standard, color index determinations are valueless. The importance of calculating the standard hemoglobin as the equivalent of 5 million red cells (since this is the number considered to be 100 per cent in the calculation of the color index) has been pointed out by Osgood, and he has introduced the term "hemoglobin coefficient" to represent "the number of grams of hemoglobin per hundred cubic centimeters of blood calculated to a red cell count of 5 million per cubic millimeters."

Accurate data for the calculation of the hemoglobin coefficient are available for 123 women, from 17 to 30. These are:

Bie and Möller[13]	10 women, averaging 14.0 Gm.
Gram and Norgaard[11]	6 women, averaging 14.0 Gm.
Rud[12]	8 women, averaging 12.8 Gm.
Haden[14]	9 women, averaging 15.7 Gm.
Osgood and Haskins[5]	100 women, averaging 14.3 Gm.
Total, 133 women, averaging 14.3 Gm.	

The average hemoglobin coefficient for the fifty women here reported is 13.97 ± 0.19, while the median is 13.94 ± 0.24 Gm. The standard deviation is $0.71 + 0.05$ Gm., and the coefficient of variation 5.1 per cent. The hemoglobin coefficient calculated on the basis of a total of 183 available accurate determinations becomes 14.2 Gm. On the basis of this coefficient recalculation of color indexes from the available accurate material shows the average indexes to be as follows:

Haden (Missouri)	9 women, averaging 1.10
Osgood and Haskins (Oregon)	100 women, averaging 1.00
Bie and Möller (Denmark)	10 women, averaging 0.99
Wintrobe (Louisiana)	50 women, averaging 0.98
Gram and Norgaard (Denmark)	6 women, averaging 0.98
Rud (Denmark)	8 women, averaging 0.90
Total, 173 women, averaging 1.	

Chart 3 is a histogram showing the frequency distribution of hemoglobin coefficients and corresponding color indexes in fifty women The mean and median coincide with the peak.

TOTAL CELL VOLUME

In determining cell volume, it is necessary to take note of the nature of the substance used to prevent clotting of the blood, as well

17. Osgood (footnote 4). Osgood and Haskins (footnote 5).

as the accuracy of the hematocrit employed and the completeness of packing of the cells. Solutions or solid substances added to the blood in order to prevent coagulation alter its isotonicity or dilute it and due allowance must be made for this. It has already been mentioned that oxalate added to blood causes a shrinkage of cell volume.

Determinations of cell volume carried out by accurate methods in normal young women from the ages of 17 to 30 are listed below. An addition of 3.5 per cent has been made to Osgood's average of 41 cc. to allow for shrinkage resulting from the addition of oxalate. No correction was necessary for the figures supplied by the other investigators quoted.

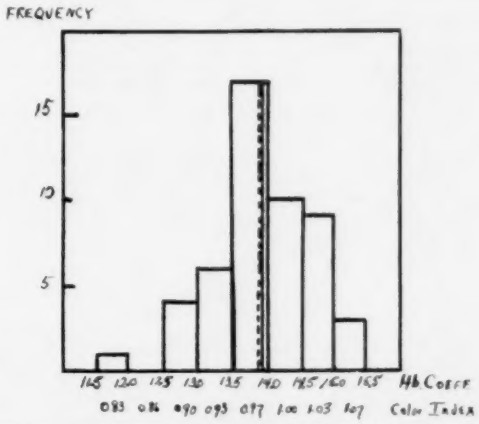

Chart 3.—Histogram showing frequency distribution of variation in hemoglobin coefficients and color indexes in fifty young women.

Gram and Norgaard[31]	6 women, averaging 40.4 cc.
Haden[34]	9 women, averaging 39.7 cc.
Gram[18]	12 women, averaging 41.0 cc.
Bie and Möller[32]	10 women, averaging 38.7 cc.
Osgood and Haskins[5]	100 women, averaging 42.4 cc.

Total, 150 women, averaging 41.7 cc. of packed red cells per hundred cubic centimeters of blood.

The average cell volume found in the fifty women examined in Louisiana was 39.5 cc. The average of the total of 200 determinations made in different parts of the world is 41.1 cc.

Chart 4 shows the frequency distribution of cell volume determinations in the fifty women examined. The mean (39.5 ± 0.19) and the median (39.3 ± 0.24) are almost identical and coincide with the peak

18. Gram, H. C.: A New Method for the Determination of the Fibrin Percentage in Blood and Plasma, J. Biol. Chem. **49**:279 (Dec.) 1921.

of the curve. The standard deviation is 2.03 ± 0.14 cc., and the coefficient of variation 5.2 per cent. Sixty-eight per cent ranged between 37 and 41.5 cc.

VOLUME COEFFICIENT AND VOLUME INDEX

Although introduced by Capps as early as 1903,[19] the importance and value of the calculation of volume index have received little attention. With the prevailing inaccurate methods of hemoglobin estimation, and the comparative simplicity and much greater accuracy of cell volume determination, the calculation of the volume index is of particular value. The information derived is, to a large extent, similar to that derived from the determination of color index while the greater accuracy of the volume index makes it particularly useful. The volume

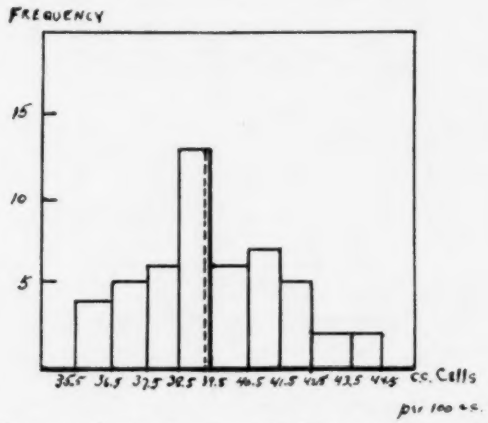

Chart 4.—Histogram showing frequency distribution of variation in cell volume in fifty young women.

index is determined by dividing the cell volume (expressed in per cent of the normal) by twice the number of red cells. As was indicated in regard to hemoglobin, a "volume coefficient" expressing the normal cell volume per five million red cells must be determined to represent 100 per cent. Volume coefficients calculated from data supplied by various authors are as follows:

Gram and Norgaard	6 women, averaging 44.0 cc.
Haden	9 women, averaging 46.2 cc.
Bie and Möller	10 women, averaging 40.8 cc.
Osgood and Haskins	100 women, averaging 44.2 cc.

Total, 125 women, averaging 44.1 cc. of packed red cells per hundred cubic centimeters of blood.

19. Capps, J. A.: A Study of Volume Index, Observations upon the Volume of Erythrocytes in Various Disease Conditions, J. M. Research **5**:367 (Dec.) 1903.

The average volume coefficient for the fifty women examined is 40.3 ± 0.16, while the median is 40.4 ± 0.21. The standard deviation is 1.76 ± 0.12, and the coefficient of variation is 4.4 per cent. The average volume coefficient, based on the total of 175 women, is 42.9 cc. This coincides closely with the volume coefficient suggested by Osgood and Haskins (42.8).

Accepting this figure of 42.8 cc. as the volume coefficient for normal women from 17 to 30 years of age, recalculation of volume indexes from the available data shows the following:

Haden	9 women, averaging 1.07
Osgood and Haskins	100 women, averaging 1.03
Gram and Norgaard	6 women, averaging 1.02
Bie and Möller	10 women, averaging 0.97
Wintrobe	50 women, averaging 0.93

Total, 175 women, averaging 1.

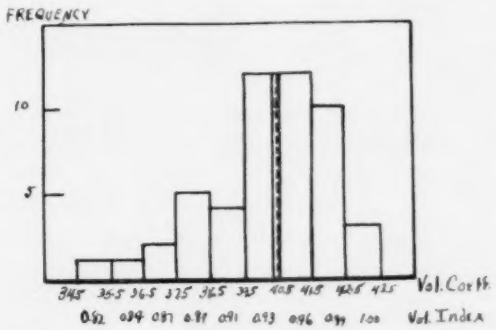

Chart 5.—Histogram showing frequency distribution of variation in volume coefficients and volume indexes in fifty young women.

Chart 5 shows the frequency distribution of volume coefficients and corresponding volume indexes in the fifty women examined. The mean and median coincide with the peak of the curve.

SATURATION INDEX

The saturation index [20] expresses the ratio of hemoglobin to the size of the red cells and is calculated by dividing the percentage of hemoglobin by the cell volume percentage. It is a true expression of the saturation of erythrocytes with hemoglobin. Supersaturation of cells with hemoglobin never occurs, according to Haden, and saturation is diminished only in certain types of anemia. In the normal the saturation index is approximately 1.

20. Wintrobe and Miller (footnote 1). Osgood (footnote 4). Osgood and Haskins (footnote 5). Haden (footnote 14).

Chart 6 shows the frequency distribution of saturation indexes of the series of women examined. Calculation of saturation indexes from available, accurate date shows the following:

Wintrobe	50	women, averaging 1.05
Haden	9	women, averaging 1.03
Bie and Möller	10	women, averaging 1.02
Osgood and Haskins	100	women, averaging 0.97
Gram and Norgaard	6	women, averaging 0.96

Total, 175 women, averaging 1.

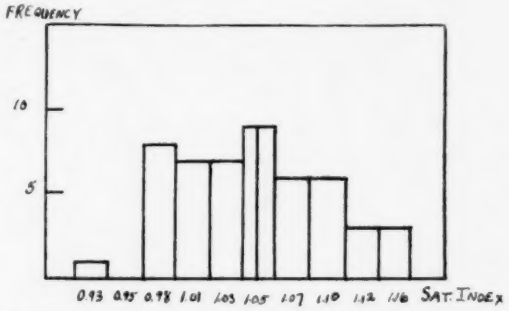

Chart 6.—Histogram showing frequency distribution of variation in saturation indexes in fifty young women.

TABLE 4.—*Observations on the Blood of Healthy Young Women from 12 to 30 Years of Age in Different Parts of the World* *

Author	Subjects: Number	Subjects: Location	Red Blood Cells in Millions	Hemoglobin: Gm.	Hemoglobin: Coefficient	Cell Volume: Cells per 100 Cc.	Cell Volume: Coefficient	Indexes: Color	Indexes: Volume	Indexes: Saturation
Osgood and Haskins [5]	100	Oregon	4.80	13.69	14.3	42.4	44.2	1.00	1.03	0.97
Wintrobe [3]	50	Louisiana	4.93	13.76	14.0	39.5	40.2	0.98	0.93	1.05
Haden [14]	9	Missouri	4.33	13.50	15.7	39.7	46.2	1.10	1.07	1.03
Bie and Möller [12]	10	Denmark	4.74	13.30	14.0	38.7	40.8	0.99	0.97	1.02
Gram and Norgaard [11]	6	Denmark	4.59	12.82	14.0	40.4	44.0	0.98	1.02	0.96
Rud [13]	8	Denmark	4.80	12.28	12.8	....	....	0.90	....	....
Bierring [10]	3	Sweden	4.24	.....	....	....	....	....	....	....
Williamson [16]	49	Illinois	....	15.11	....	....	....	....	....	....
Gram [15]	25	Denmark	....	.....	....	41.0	....	....	....	....
Averages			4.78	13.91	14.2	41.0	42.9	1.00	1.00	1.00

* Calculations are based on a hemoglobin coefficient of 14.2 Gm. and a volume coefficient of 42.8 cc.

TABLE 5.—*Summary of Blood Determinations in Young Men and Women Residing in the Southern States*

Subjects	Red Blood Cells in Millions	Hemoglobin: Gm.	Hemoglobin: Coefficient	Cell Volume: Cc.	Cell Volume: Coefficient
100 Men	5.85	17.00	14.5	46.5	40.0
50 Women	4.93	13.70	14.0	39.5	40.2

SUMMARY AND CONCLUSIONS

1. Blood determinations in fifty healthy young women from the ages of 17 to 30 residing in the southern states have been carried out with the object of investigating the hypothesis that an anemia of purely climatic origin is present in otherwise healthy persons residing in tropical and subtropical climates and is the cause of the pallid appearance of many of these persons, and, secondly, in order to furnish further data from which to calculate normal blood standards.

2. The results of these determinations may be summarized as follows:

(a) The average red cell count was 4,930,000 per cubic millimeter with 76 per cent between 4,640,000 and 5,220,000.

(b) The average amount of hemoglobin was 13.76 Gm. per hundred cubic centimeters of blood with 68 per cent between 12.77 and 14.75 Gm.

(c) The average hemoglobin coefficient was 13.97 Gm.

(d) The average volume of packed red cells was 39.5 cc. per hundred cubic centimeters of blood with 68 per cent between 37 and 41.5 cc.

(e) The average volume coefficient was 40.3 cc.

3. Like the results of blood determinations in men residing in a subtropical climate, these results lend no support to the hypothesis that a physiologic anemia exists in such a climate.

4. The average normal figures for young women from 17 to 30, based on a number of accurate determinations in different parts of the world, are 4,780,000 red cells per cubic millimeter, 13.9 Gm. of hemoglobin and 41.1 cc. of packed red cells per hundred cubic centimeters of blood. The average hemoglobin coefficient is 14.2 Gm., and the average volume coefficient is 42.9 cc.

THE CLINICAL VALUE OF TESTS OF LIVER FUNCTION *

E. F. FOLEY, M.D.
CHICAGO

This study is an effort to evaluate clinically certain so-called tests of liver function on the basis of the results obtained from their use in cases of known or anticipated diseases of the liver. The difficulties encountered in the application of functional tests to the liver have been commented on frequently in recent literature and have been concisely summarized by Carlson.[1] A critical survey of the many liver function tests which have been introduced led Mann and Bollman [2] to the conclusion that the tests which offered the greatest clinical possibilities were those concerned with the measurement of serum bilirubin and the excretion of specific dyes. These observations have been supported in general by the workers who have applied the tests to clinical material, the van den Bergh reaction and the icterus index being used in the study of serum bilirubin and one of the halogenated phenolphthaleins as the specific dye.

These tests deal with functions which are entirely excretory in nature: in one instance, the excretion of a product which is normally eliminated by the liver, and in the other instance, a foreign substance (dye) which happens to be specifically removed by the liver. Since the biliary passages are an indispensable part of the excretory unit of the liver, Murphy [3] suggested that these tests be considered as biliary function tests.

The clinical use of the van den Bergh reaction and the icterus index has led to the establishment of a normal range of serum bilirubin which varies within somewhat narrow limits according to the results obtained by various workers. Thus the van den Bergh test,[4] with the diazo reagent, gave from 0.1 to 0.25 mg. per hundred cubic centimeters of blood as the

* Submitted for publication, Oct. 27, 1928.

* From the Department of Medicine, Research and Educational Hospital, University of Illinois.

1. Carlson, A. J.: Physiology of Liver: Present Status of Our Knowledge, J. A. M. A. **85**:1468 (Nov. 7) 1925.

2. Mann, F. C., and Bollman, J. L.: Liver Function Tests, Arch. Path. & Lab. Med. **1**:681 (May) 1926.

3. Murphy, W. P.: Boston M. & S. J. **194**:297, 1926; Biliary System Function Tests, Arch. Int. Med. **37**:797 (June) 1926.

4. Van den Bergh, A. A. Hijmans: Presse méd. **29**:441, 1921.

average values obtained in normal persons; Andrewes,[5] Lepehne,[6] McNee,[7] Ravdin,[8] Hall,[9] Hazelhorst[10] and Steen[11] agreed substantially with these figures. Schiff[12] found that in the majority of his cases there was 0.8 mg. per hundred cubic centimeters or less and considered 1 mg. as the upper limit, allowing 0.2 mg. for fluctuation during the day. Greene and his co-workers[13] set 2 mg. per cent as the upper limit of normal, thus including cases of physiologic hyperbilirubinemia. In 35 per cent of the normal serums examined by Feigl and Querner,[14] no measurable color change occurred. Since the color standard represents the color developed by a bilirubin concentration of 1:200,000 or 0.2 mg. per cent, these serums contain less than 0.2 mg. per cent. Similar results were obtained by Hazelhorst[10] in 33 per cent of his cases, by Schiff[12] in 34 per cent and by Steen[11] in 82 per cent. That the direct reaction occurs in cases of frank obstructive jaundice and the indirect in normal cases and in cases of hemolytic jaundice is fairly well conceded though the differential diagnostic value is not so generally accepted. Thus Greene and his co-workers[13] used the indirect reaction merely as a means of developing the measurable color for the quantitative estimation of serum bilirubin.

With the icterus index, the normal values have been more definitely established. Meulengracht,[15] and later Bernheim,[16] found the majority of normal values to range from 3 to 5, while hyperbilirubinemia, insufficient to produce clinical icterus, gave results from 6 to 16 and frank jaundice above 30. Later, Bernheim[17] showed that cases of severe secondary anemia were associated with hypobilirubinemia with values of less than 3. Objections have been raised to the icterus index because slight changes of the color of the serum may result from other

5. Andrewes, C. H.: Quart. J. Med. **18**:19 (Oct.) 1924.

6. Lepehne, G.: Deutsches Arch. f. klin. Med. **132**:96, 1926.

7. McNee, J. W.: Brit. M. J. **1**:716, 1922.

8. Ravdin, E. G.: Am. J. M. Sc. **169**:850, 1925.

9. Hall, W. W.: U. S. Nav. M. Bull. **24**:843, 1926.

10. Hazelhorst: J. Lab. & Clin. Med. **12**:529, 1927.

11. Steen, R. E.: Irish J. M. Sc., 1927, p. 573.

12. Schiff, L.: Serum Bilirubin in Health and in Disease, Arch. Int. Med. **40**:800 (Dec.) 1927.

13. Greene, C. H.; Snell, A. M., and Walters, W.: Diseases of the Liver: Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248 (Aug.) 1925.

14. Feigl, J., and Querner, E.: Ztschr. f. d. ges. exper. Med. **9**:153, 1919.

15. Meulengracht, E.: Bilirubin Colorimeter, Deutsches Arch. f. klin. Med. **137**:38, 1921; Abstr. J. A. M. A. **77**:1141 (Oct. 1) 1921.

16. Bernheim, A. R.: Icterus Index (A Quantitative Estimation of Bilirubinemia): Aid in Diagnosis and Prognosis, J. A. M. A. **82**:291 (Jan. 26) 1924.

17. Bernheim, A. R.: Significance of Variations of Bilirubinemia, Arch. Path. & Lab. Med. **1**:747 (May) 1926.

pigments than bilirubin, notably carotin and luetin and to the difficulty occasionally encountered in matching the pale yellow of the lower dilutions.

PROCEDURE

Thirty minutes after the intravenous injection of the required amount of bromsulphalein (2 mg. per kilogram of body weight) about 10 cc. of blood was drawn, special care being taken to avoid even a trace of hemolysis. After allowing the sample to clot and after centrifugation, the serum was pipeted off and divided into three small tubes. One of these was compared directly with the proper permanent standard of potassium dichromate prepared according to the method recommended by Murphy [3] for the icterus index. The second was alkalinized with 10 per cent sodium hydroxide to develop the color of the dye. This was then matched with the standards of the dye, the sample which had previously served for the icterus index being used as the control. The third specimen was used for the van den Bergh test which was performed according to the modification of Thannhauser and Anderson.[18] The presence of the unalkalinized dye did not interfere with the reaction.

One hundred patients used as controls were selected from the outpatient department of the Research and Educational Hospital; they were apparently free from gross pathologic changes of the liver. Particular attention was taken to exclude cases in which a history of alcoholism or syphilis was obtained. No attempt was made to group the values for serum bilirubin according to age, since Perkin [19] found no appreciable variation. In the control cases the diazo reaction was of the indirect type, and in thirty-eight cases the color developed was so faint as to be unmeasurable as compared with the standard, and hence contained less than 0.2 mg. per cent. The maximum value obtained in these cases was 1.8 mg. per cent in a medical student who for years was repeatedly told that he "looked yellow." Careful investigation failed to reveal any pathologic changes in either the liver or the hematopoietic system to account for the hyperbilirubinemia, and he was considered to have a case of physiologic hyperbilirubinemia similar to that reported by Gilbert and Lereboullet,[20] van den Bergh,[4] Schiff,[12] Snell and others. In the majority of the cases (71 per cent) the values were less than 0.3 mg. per cent, and in 95 per cent they were less than

18. Thannhauser, J. S., and Anderson, E.: Deutsches Arch. f. klin. Med. **137**:179, 1921.

19. Perkin, F. S.: Blood Bilirubin: Estimation and Clinical Significance, Arch. Int. Med. **40**:195 (Aug.) 1927.

20. Gilbert, A., and Lereboullet, P.: Comp. rend. Soc. de biol. **58**:937, 1905; quoted by van den Bergh: Presse méd. **29**:44, 1921; quoted by Schiff: Arch. Int. Med. **40**:800 (Dec.) 1927.

0.5 mg. per cent. The maximum reading, excluding the case of physiologic hyperbilirubinemia mentioned, was 0.78 mg. per cent.

The icterus index in 99 per cent of the cases was 6 or less, and in three cases it was 2. In the cases of physiologic hyperbilirubinemia, the reading was 8. The average reading in 100 cases was 4.02. The dye used was bromsulphalein, which was introduced by Rosenthal and

TABLE 1.—*Cardiac Failure with Passive Congestion of the Liver*

Number	Jaundice	Liver Edge, Cm.	Bile in Urine	Hemoglobin	Red Blood Cells	Icterus Index	Direct Van den Bergh Test	Serum Bilirubin	Dye, per Cent	Clinical Type
1.....	Slight	3	Trace	65	4,200	20	+	2.9	20	Rheumatic
2.....	Soft palate	6	0	80	400	18	+	2.5	20	Rheumatic
3.....	Soft palate	3	0	70	4,200	11	+D	2.1	15	Rheumatic
4.....	Soft palate	4	Trace	75	3,610	16	+D	2.1	20	Rheumatic
5.....	Soft palate	3	0	75	4,400	12	+	1.8	15	Rheumatic
6.....	Soft palate	5	0	83	4,900	10	+	1.8	15	Rheumatic
7.....	Soft palate	3	0	85	4,600	10	+	1.8	15	Rheumatic
8.....	0	4	0	78	3,800	8	0	1.3	10	Rheumatic
9.....	0	3	0	80	4,100	8	0	1.1	5	Rheumatic
10.....	0	2	0	75	3,750	5	0	0.9	5	Rheumatic
11.....	0	3	0	60	3,700	6	0	0.8	10	Rheumatic
12.....	0	3	0	90	4,310	6	0	0.8	5	Rheumatic
13.....	0	2	0	72	4,100	7	0	0.6	5	Rheumatic
14.....	0	3	0	85	4,200	5	0	0.6	10	Rheumatic
15.....	0	3	0	60	2,650	5	0	0.5	10	Rheumatic
16.....	Slight	2	Trace	72	3,650	18	+	2.6	25	Syphilitic
17.....	Soft palate	2	0	90	4,950	8	+	1.8	10	Syphilitic
18.....	Soft palate	2	0	65	4,756	12	+	1.6	15	Syphilitic
19.....	0	2	0	65	3,100	6	0	0.8	15	Syphilitic
20.....	0	1	0	70	3,850	6	0	0.8	10	Syphilitic
21.....	0	2	0	90	4,100	6	0	0.61	15	Syphilitic
22.....	0	2	0	90	5,800	8	0	0.6	10	Syphilitic
23.....	0	3	0	80	3,900	7	0	0.52	10	Syphilitic
24.....	0	2	0	65	4,150	5	0	0.5	5	Syphilitic
25.....	0	2	0	71	4,100	6	0	0.4	10	Syphilitic
26.....	0	3	0	75	4,610	13	0	0.9	20	Myocardial nephritis
27.....	0	3	0	77	5,100	11	0	0.8	15	Myocardial nephritis
28.....	++	3	+	70	3,800	83	+	8.7	40	Rheumatic alcoholism
29.....	+	3	+	80	4,100	56	+	5.1	30	Rheumatic alcoholism
30.....	+	3	+	60	2,100	24	+D	2.9	25	Myocardial cirrhosis
After compensation.....	0	3	0	..	.....	10	0	1.8	20	

White. None of the reactions which condemned the use of phenoltetrachlorphthalein was noted in any of the cases. In the control cases no dye was retained in the serum thirty minutes after injection.

CARDIAC FAILURE WITH PASSIVE CONGESTION OF THE LIVER

There were thirty patients in the groups with cardiac failure who presented the typical picture of broken compensation with tender enlargement of the liver. Seventeen of these cases were on a rheumatic basis, two patients had aortic as well as mitral involvement, two gave

a history of drinking heavily just prior to the onset of symptoms and were jaundiced, and one had evidence of a cirrhosis following the establishment of compensation. Ten were syphilitic: one of these was jaundiced and had, as found at postmortem examination, a primary aortitis (Rappaport [21]), and two had a myocardial condition on the basis of a chronic nephritis.

Of the rheumatic cases, except the alcoholic, eight terminated fatally, five of which gave direct reactions, two being delayed, with serum bilirubin values from 1.8 to 2.9 mg. The patient with the highest reading was found clinically to be slightly jaundiced; six had definite discoloration of the soft palate. The icterus index reading in these cases was from 10 to 29, showing a decided increase over normal. The development of jaundice as an unfavorable prognostic sign in cardiac

TABLE 2.—*Portal Cirrhosis with Ascites*

Number	Jaundice	Liver Edge, Cm.	Bile in Urine	Hemoglobin	Red Blood Cells in Millions	Icterus Index	Direct Van den Bergh Test, Mg. per Cent	Serum Bilirubin, per Cent	Dye, per Cent
607	0	0	Negative	40	2.100	5	Negative	0.5	10
662	0	0	Negative	51	2.800	7	Negative	0.6	15
2859	0	Palpable	Negative	45	2.200	9	Negative	1.1	25
4828	0	3	Negative	48	3.100	8	+	1.8	15
103	0	2	Negative	55	3.000	5	Negative	0.8	15
4198	0	0	Negative	51	3.040	12	Negative	0.9	25
1108	0	0	Negative	75	3.150	9	Negative	1.4	20
1429	0	1	Negative	70	3.250	7.5	Negative	0.4	5
0008	0	0	Negative	65	2.900	6	Negative	0.9	25
1008	0	0	Negative	60	3.100	8	+	1.2	30
G. E.	0	0	Negative	50	2.100	6	Negative	0.4	15
C. C.	0	?	?	55	3.160	7	Negative	0.6	20
F.	0	Palpable	Negative	65	3.180	9	Negative	1.5	10
A. P.	0	0	0	70	3.650	8	Negative	0.9	10

decompensation has long been recognized clinically. The other fatal case had the lowest reading, 0.5 mg. per cent; the patient, however, had involvement of both the mitral and the aortic orifices and ran the typical course of a recurrent endocarditis.

In the syphilitic cases, direct reactions with readings of from 1.6 to 2.6 mg. per cent and icterus indexes of from 8 to 18 were obtained in three cases which terminated in death. In the other cases the readings of from 0.4 to 0.8 mg. and indexes of from 5 to 8 had a tendency to be on a lower level than those obtained in mitral lesions. The tendency of the higher readings to be more common in the mitral lesions has been commented on by Fishberg,[22] Meulengracht [23] and Schiff.[12] In one of the two alcoholic patients with cardiac decompensation, the

21. Rappaport, B. Z.: Primary Acute Aortitis, Arch. Path. & Lab. Med. **2**:653 (Nov.) 1926.

22. Fishberg, A. M.: Jaundice in Myocardial Insufficiency, J. A. M. A. **80**:1516 (May 26) 1923.

23. Meulengracht, E.: Deutsches Arch. f. klin. Med. **132**:285, 1920.

cardiac breakdown was definitely attributed to the exposure resulting from recent and frequent intoxication. In these cases a prompt direct reaction was obtained with relatively high readings. The recovery of these patients would indicate that the jaundice was not a direct result of the cardiac failure. Concomitant jaundice offers no such serious prognosis as does jaundice resulting directly from cardiac failure.

In the cases of cardiac failure with secondarily contracted kidneys, the icterus indexes have a tendency to be higher than the figures for serum bilirubin obtained with the diazo reagent; this can probably be

TABLE 3.—*Carcinoma*

Number		Jaundice	Liver Edge, Cm.	Bile in Urine	Hemoglobin	Red Blood Cells in Millions	Icterus Index	Direct Van den Bergh Test	Serum Bilirubin, Mg. per Cent	Dye, per Cent	Postmortem Diagnosis
1147	(1)	4	3; mass in right upper quadrant	+	40	3.160	63	+	27.7	15	Adenocarcinoma of gallbladder
6655	(2)	1	1	+	65	3.800	46	+	6.9	40	
6655	(2)	4	2	+	50	3.100	115	+	22.9	65	
6655	(2)	4	2	+	50	2.900	164	+	35.4	80	Carcinoma of head of pancreas
694	(3)	4	3; mass in right upper quadrant	+	30	2.800	110	+	26.3	65	Carcinoma of pancreas
5586	(5)	0	1	0	60	3.200	4	0	0.6	0	Carcinoma of stomach; metastases to liver
1635	(6)	0	1	0	50	3.000	3	0	0.3	0	Carcinoma of stomach; metastases to liver
1700	(7)	0	Not palpable	0	20	2.000	5	0	0.8	0	Carcinoma of stomach; metastasis to liver
1783	(10)	0	Not palpable	0	71	3.730	3	0	0.6	0	Carcinoma of esophagus
3450	(11)	0	Not palpable	0	55	3.100	3	0	0.2	0	Carcinoma of sigmoid
5883	(8)	0	Not palpable	0	35	3.000	3	0	0.2	0	Carcinoma of ovary and metastasis to liver
P	(12)	0	2	0	40	2.800	8	0	0.5	5	Retroperitoneal sarcoma
1612	(9)	0	0	0	45	3.000	4	0	0.3	0	Lymphosarcoma; metastases to liver
8494	(13)	0	0	0	75	4.101	6	0	0.4	0	Hypernephroma
	(14)	0	0	0	70	4.080	7	0	0.5	0	Carcinoma of prostate
	(4)	4	4	+	71	3.510	116	+	17.0	55	Carcinoma of head of pancreas

explained on the basis of the retention of some pigment other than bilirubin in the serum which is usually excreted through the kidneys. In all cases of cardiac failure the dye test indicated a definite retention varying from 5 to 25 per cent. The exact aid which these tests offer to the clinician in cases of cardiac decompensation seemed to be prognostic. In those cases in which the clinical symptom of jaundice occurs, no laboratory test is necessary to confirm this fact, but in the borderline cases of clinical jaundice, in which it is not possible to decide clinically whether the skin of the patient is icteric or merely sallow, estimation of serum bilirubin is of definite value. The dye test in itself merely indicates a moderately severe dysfunction of the liver, but to it can be attributed no particular diagnostic or prognostic aid in cases of cardiac failure.

In ten cases of catarrhal jaundice, prompt direct reactions were obtained with high values of serum bilirubin and marked retention of dye. The retention of dye seems to parallel to a certain extent the serum bilirubin, as noted by Greene and his co-workers [13] in experimentally produced obstructive jaundice. Rosenthal and White [24] showed that the retention of dye in experimental animals bore a direct relationship to the amount of liver tissue removed. In one of these cases the retention amounted to 90 per cent. While this degree of retention, together with the severe hyperbilirubinemia, indicates a diffuse lesion, it serves to show that all functions are not equally affected. The vital metabolic functions are apparently spared, for even though the liver possesses a factor of safety amounting to 75 per cent, with severe

TABLE 4.—*Disease of the Gallbladder*

Case	Diagnosis	Diagnosis Made by	Jaundice	Bile in Urine	Icterus Index	Direct Van den Bergh Test	Serum Bilirubin, Mg. per Cent	Dye, per Cent
5514	Chronic cholecystitis; fibrosis	Operation	0	0	12	+	1.4	0
7937	Chronic cholecystitis	Operation	±	0	17	+	1.9	0
2137	Subacute and chronic cholecystitis	Operation	0	0	12	+	1.4	0
61686	Subacute and chronic cholecystitis	Operation	0	0	11	0	1.1	0
2282	Stone obstructing common duct	Clinical course and operation	4	+	60	+	15.8	30
3821	Cholecystitis with stone	Graham Cole	0	0	7	0	1.0	0
3148	Cholecystitis with stone	Graham Cole	0	0	8	0	0.4	0
2137	Cholecystitis with stone	Graham Cole	0	0	6	0	0.4	0
6030	Cholecystitis with stone	Graham Cole	0	0	4	0	0.3	0
6214	Cholecystitis with stone	Graham Cole	0	0	3	0	0.2	0

impairment of one function, it would be expected that the patient would be more sick than he is with catarrhal jaundice if all functions were similarly disturbed. Frequent repetitions of the serum bilirubin estimation shows definite changes in the icteric index not apparent in the skin. The injection of bromsulphalein does not increase the serum bilirubin in catarrhal jaundice, indicating that this dye does not offer any further insult to the already injured liver.

Similar results were obtained in cases of "arsphenamine jaundice," with the exception that higher values were more common. There were five patients with severe jaundice, graded 4, clinically. In all a direct positive reaction was obtained with values for serum bilirubin from 16.3 to 35 mg. per cent. The icterus index similarly showed high values, from 95 to 195. The retention of dye seems to parallel to a certain degree the retention of bilirubin. In this connection, patients

24. Rosenthal, S. M., and White, E. C.: Clinical Application of Bromsulphalein Test of Hepatic Function, J. A. M. A. **84**:1112 (April 11) 1925.

under antisyphilitic treatment in the Dermatological Dispensary of the Research and Educational Hospital who are suspected of having disease of the liver are followed up at regular intervals. Gerrard [25] noted that the administration of arsphenamine is frequently associated with evidence of latent icterus or hyperbilirubinemia. Three such cases which have been followed up for three, six and nine months, respectively, are included. While none of these patients had the severe clinical picture of intense jaundice seen in the other cases, it is interesting to note the duration of hyperbilirubinemia. It is possible that these patients may later develop a type of cirrhosis. In this field the tests of

TABLE 5.—*Results in Pernicious Anemia Before and After Diet*

Number	Date	Hemoglobin	Red Blood Cells	Icterus Index	Direct Van den Bergh	Indirect Van den Bergh	Dye
9834	May 19, 1928	21	0.660	14.0	0	1.8	0
	June 28, 1928	54	3.610	4.1	0	0.5	0
9838	May 11, 1928	38	1.070	8.0	0	0.61	0
	June 28, 1928	49	2.430	7.8	0	0.45	0
9833	May 19, 1928	26	1.330	10.0	0	0.9	0
	June 21, 1928	46	3.200	4.0	0	0.38	0

TABLE 6.—*Hemolytic Icterus*

Number	Jaundice	Liver Edge, Cm.	Spleen	Hemoglobin	Red Blood Cells in Millions	Icterus Index	Increased Fragility	Direct Van den Bergh	Serum Bilirubin, Mg. per Cent	Dye Test
1	±	2	6 cm.	45	3.20	24.0	+	0	2.9	0
After operation	0	2	650 Gm.	75	3.60	6.0	—	0	0.5	0
2	+	2	7 cm.	58	3.02	32.0	+	0	3.8	0
After operation	0	2	750 Gm.	80	3.90	5.0	—	0	0.45	0
3	+	2	4	50	3.10	16.0	+	0	2.1	0
4	0	4	6	64	3.95	17.5	+	0	2.6	0

function, particularly the estimation of bilirubin, are highly commended, for they readily detect the presence of one of the absolute contraindications for the administration of the arsenicals.

A few cases of severe fatty liver with jaundice resulting from alcohol are included at this time. The results obtained here are similar to those obtained in the arsenical group. In all there was the history of heavy drinking, inability to eat and sleep and finally the development of visual hallucinations. In addition to the jaundice and the extreme restlessness, examination revealed a large soft liver with a definitely rounded edge. A series of similar cases was reported by LeCount and Singer,[26] in which they ascribed the cause of death to a failure of the glycogenic function of the liver.

25. Gerrard, W. I.: Brit. M. J. **1**:224, 1924.

26. LeCount, E. R., and Singer, H. A.: Fat Replacement of Glycogen in the Liver as a Cause of Death, Arch. Path. & Lab. Med. **1**:84 (Jan.) 1926.

PORTAL CIRRHOSIS WITH ASCITES

In this group there were fourteen cases presenting the clinical picture of advanced cirrhosis with marked ascites requiring paracentesis at frequent intervals. In five the liver was enlarged, and in eight it was not palpable. In five, serum bilirubin values of 1 + mg. per cent were obtained; in nine, there was less than 1 mg. per cent—normal or high normal values. In twelve, the icterus index was in the zone of latent icterus. In all, however, there was definite retention of dye varying from a minimum of 5 per cent to a maximum of 25 per cent. The gross pathologic picture of this type of liver would lead one to expect marked impairment in function. That this does not occur has been explained

TABLE 7.—*Arsphenamine Jaundice*

	Jaundice	Liver Edge	Bile	Icterus Index	Direct	Serum Bilirubin, Mg. per Cent	Dye
1	4	8	+	195	+	35.9	85
2	4	6	+	175	+	35.1	90
3	4	3	+	125	+	25.4	85
4	4	4	+	116.3	+	19.2	70
5	4	4	+	95	+	16.3	45
6	±	1	+	34	Delayed +	4.2	15
10 days	±	1 cm.	0	15	Delayed	2.1	5
1 month	—	1	0	12	Delayed	1.9	5
6 months	—	1	0	12	Delayed	1.8	Trace
9 months	—	1	0	8	0	1.6	0
7	±	1 cm. on deep inspiration	0	18	Delayed	2.6	5
1 month	—	1 cm. on deep inspiration	0	12	Delayed	2.1	5
2 months	—	1 cm. on deep inspiration	0	9	0	1.5	5
3 months	—	1 cm. on deep inspiration	0	7	0	1.1	Trace
8	±	Palpable	0	21	±	2.4	10
6 weeks	—	Palpable	0	14	Delayed	1.5	5
3 months	—	Palpable	0	9	Delayed	0.9	5
6 months	—	Palpable	0	6	0	0.5	0

by Greene and his associates [27] by the chronicity of the process which allows time for regenerative changes to occur. There is a definite disproportion between the results obtained with the dye test and those with the measurement of serum bilirubin. The higher values obtained with the dye test would suggest that the regenerative changes which occur compensate to a greater extent for the normal function of the excretion of bilirubin than for the artificial function of the excretion of dyes.

CARCINOMA INVOLVING THE LIVER

Only those cases of carcinoma are included in which postmortem examination or operation definitely proved involvement of the liver. Four of the fourteen cases were associated with jaundice which, as

27. Greene, C. H.; McVicar, C. S.; Snell, A. M., and Rowntree, L. G.: Diseases of the Liver: Further Studies in Experimental Obstructive Jaundice, Arch. Int. Med. **40**:159 (Aug.) 1927.

indicated by the van den Bergh test was of the obstructive type. In these cases high icterus indexes were obtained, as well as marked retention of dye. In six cases of secondary carcinoma of the liver, the dye test was negative, and in only one of these was there an increase of serum bilirubin. The usual secondary anemia was present in all cases which, according to Bernheim,[17] is associated with hypobilirubinemia. In one case, that of a man who because of jaundice was referred from the department of syphilology where he had presented himself for antisyphilitic treatment, repeated examination showed a high grade progressive type of obstructive jaundice. Postmortem examination revealed a carcinoma of the head of the pancreas with biliary obstruction. Positive results indicate the presence of metas-

TABLE 8.—*Catarrhal Jaundice*

Number	Jaundice	Liver Edge, Cm.	Bile in Urine	Icterus Index	Van den Bergh Direct	Serum Bilirubin	Dye
1.....	4	8	+	125	+	22.6	90
10 days later....	3	5	+	90	+	17.2	65
2.....	4	7	+	110	+	19.2	70
5 days later.....	4	7	+	85	+	16.2	50
3.....	4	7	+	96	+	20.6	55
5 days later.....	3	5	+	90	+	18.2	40
4.....	4	6	+	91	+	17.4	65
5.....	4	6	+	90	+	19.2	60
Next day.....	4	6	+	90	+	20.1	60
Next day.....	4	6	+	88	+	20.1	60
Next day.....	4	6	+	83	+	19.4	60
1 week later.....	4	6	+	70	+	15.1	50
6.....	4	4	+	68	+	12.0	55
7.....	4	2	+	55	+	11.1	50
8.....	4	2	+	46	+	7.1	30
9.....	4	5	+	45	+	4.2	25
10.....	4	0	+	30	+	3.8	35
11.....	4	3	+	28	+	3.5	25

tases to the liver, but negative results are not conclusive evidence of their absence.

Diseases of the gallbladder present the greatest field for the clinical application of these tests, for in the diagnosis of painful conditions of the upper part of the abdomen, the presence or absence of even a slight degree of jaundice bears great weight. By means of these tests it is possible to show the presence of hyperbilirubinemia before icterus is present clinically. In these ten cases, the diagnosis was confirmed in five by operation and in five by the Graham Cole method of cholecystography. Two of these patients were icteric; four gave a direct positive reaction; six showed hyperbilirubinemia, while four gave normal values for serum bilirubin. In only one was the dye test positive. In seven increased values were obtained with the icterus index. The failures occurred in cases in which the diagnosis of stone in the gallbladder was made by cholecystography, and in which there was apparently no obstruction to the biliary excretion.

The presence of latent icterus as determined by the measurement of the serum bilirubin is a practical help in cases in which disease of the gallbladder is suspected. In chronic disease of the gallbladder, however, whether due to cholelithiasis or to a chronic inflammatory condition, there may be periods in which latent icterus is not present. At such times the bilirubin tests offer no diagnostic help. Bernheim [17] found that there is a latent icterus in cases of duodenal ulcer. This observation reduces the value of these tests in the diagnosis of pain in the upper part of the abdomen.

TABLE 9.—*Fatty Liver (Alcoholic)*

Number	Jaundice	Liver Edge, Cm.	Hemoglobin	Red Blood Cells in Millions	Icterus Index	Direct Van den Bergh	Serum Bilirubin	Dye
1	4	7	80	3.600	118	+	10.1	75
2	4	8	75	4.100	76	+	8.1	80
3	3	7	75	3.500	80	+	6.5	80
4	2	6	85	3.800	60	+	4.8	65

TABLE 10.—*Diseases of the Blood*

Number	Hemoglobin	Red Blood Cells	Icterus Index	Van den Bergh Direct	Serum Bilirubin	Dye	Diagnosis
7743	23	0.999	16	0	2.2	0	Pernicious anemia
1083	38	1.68	15	0	2.2	0	Pernicious anemia
3731	37	1.45	12	0	1.8	0	Pernicious anemia
	24	0.680	14	0	1.8	0	Pernicious anemia
736	30	1.25	13	0	1.6	0	Pernicious anemia
2073	25	1.01	12	0	1.4	0	Pernicious anemia
7615	30	1.20	11	0	1.1	0	Pernicious anemia
4305	38	1.80	10	0	0.9	0	Pernicious anemia
	26	1.330	10	0	0.9	0	Pernicious anemia
2084	36	1.72	8	0	0.9	0	Pernicious anemia
1140	55	2.16	8	0	0.8	0	Pernicious anemia
6319	39	1.80	6	0	0.6	0	Pernicious anemia
2161	50	3.32	3	0	0.3	0	Myeloid leukemia
3923	55	3.75	3	0	0.2	0	Myeloid leukemia
1537	40	3.55	2	0	0.2	0	Myeloid leukemia
5209	35	2.10	1	0	0.2	0	Myeloid leukemia
2140	140	7.20	4	0	0.4	0	Polycythemia vera
1568	120	6.50	6	0	0.4	0	Polycythemia vera

In twelve cases of pernicious anemia, ten showed latent icterus with readings from 8 to 18 and serum bilirubin values from 0.6 to 2 mg. per cent. In all the diazo reactions were of the indirect type. None of the cases presented dye retention. In three cases in which remissions were induced by liver diet, subsequent estimations gave normal results. The hyperbilirubinemia occurring in pernicious anemia has been universally accepted. McNee [28] explained the excess of bilirubin which gives the indirect reaction on the basis of supersaturation of the serum resulting from excessive destruction of erythrocytes to such a degree that the excretory power of the liver is exceeded.

28. McNee, J. W.: Quart. J. Med. **16**:390, 1923.

In the period of remission as induced by liver diet, the return to normal values would be expected on the basis of McNee's explanation indicating a decrease in the hemolysis. It would seem, then, that icterus from bilirubinemia which gives the indirect reaction and negative dye test is characteristic of a hemolytic process. This combination of results does not indicate so much a disease process in the liver itself as it measures the excretory efficiency of the reserve power of the liver under stress.

In four cases of hemolytic icterus, latent icterus ranging from 16 to 30 occurred with indirect serum bilirubin values of from 2.1 to 3.8 mg. per cent. In these cases as in pernicious anemia, there was no retention of dye. In all cases there was increased fragility of the erythrocytes. In two cases in which splenectomy was done, the weights of the spleen were 650 and 750 Gm. The serum bilirubin dropped from 2.9 to 0.5 mg. per cent and from 3.8 to 0.45 mg. per cent following splenectomy.

TABLE 11.—*Results in Normal Cases*

Number of Cases	Serum Bilirubin	Number of Cases	Icterus Index
38	—0.2	3	2
33	0.2 to 0.29	41	3
16	0.3 to 0.39	20	4
9	0.4 to 0.49	23	5
2	0.5 to 0.6	13	6
1	0.6 to 0.7		
1	0.7 to 0.8		
1	1.8 mg. per cent		
	Average 4.02		

SUMMARY

The measurement of serum bilirubin in 100 apparently normal cases by means of the quantitative van den Bergh reaction gave values ranging from a minimum of less than 0.2 mg. per cent to a maximum of 1 mg. per cent, with, however, the largest portion (87 per cent) with readings of less than 0.4 mg. per cent. In the same cases the average icterus index reading was 4.02, with a minimum reading of 2 and a maximum of 6. In all these cases, 2.2 mg. of bromsulphalein, injected intravenously, was removed from the serum in thirty minutes, without either systemic or local reactions.

Retention of dye and bilirubin occurred regularly in the cases of passive congestion of the liver resulting from cardiac decompensation.

The results obtained in various types of lesions of the heart showed no great difference. Though collectively the readings showed an inclination to be on a slightly higher level in mitral lesions, the individual variations was not sufficient to be of diagnostic value.

In catarrhal jaundice and in the jaundice following the use of arsenicals and alcohol, a high degree of retention of both dye and

bilirubin was obtained. The bilirubin from these various types of jaundice gave no characteristic difference in their behavior to the diazo reagent.

In all diseases of the gallbladder associated with frank jaundice, retention of dye occurred, but not in the cases in which a latent icterus was present. Not all cases of proved disease of the gallbladder showed a latent icterus.

Low values of serum bilirubin occurred in carcinoma in general. High values were encountered in cases in which metastases caused an obstructive jaundice.

In cirrhosis of the liver the serum bilirubin tests gave unexpectedly low values compared to the high degree of dye retention.

In cases of hemolytic icterus and pernicious anemia, an increase in the serum bilirubin was noted with an indirect diazo reaction and a negative dye test. Splenectomy in two cases of hemolytic icterus was followed by a return of the serum bilirubin to normal.

CONCLUSION

The use of bromsulphalein in the doses usually employed is devoid of local or systemic reaction. The retention of this dye occurs only in diseases of the liver.

The modification of the icterus index as suggested by Murphy commends itself for simplicity without the sacrifice of accuracy. The icterus index gives a numerical index of the degree of yellow discoloration of the serum, which may result from disease of the liver or disturbances in the bilirubin metabolism apart from the liver.

The diazo reagent differentiates between the bilirubinemia occurring as a result of disease of the biliary system, whether intrahepatic or extrahepatic, and the bilirubinemia occurring in disturbances of the reticulo-endothelial system characterized by increased destruction of erythrocytes.

These tests give an index of the vital metabolic functions of the liver only so far as these functions are paralleled by the excretory functions.

The tests are a valuable addition to the diagnostic equipment, but, like laboratory tests generally, are subject to wide variations in interpretation.

Book Reviews

THE FEMALE SEX HORMONE. Part I. Biology, Pharmacology and Chemistry. Part II. Clinical Investigations Based on the Female Sex Hormone Blood Test. By Robert T. Frank, A.M. M.D., F.A.C.S., Gynecologist to Mount Sinai Hospital, New York. Price, $5.50. Pp. 331, with 86 illustrations and 36 graphs. Springfield, Ill.: Charles C. Thomas, 1929.

The author says "In this monograph there is no thesis to defend. The sole object actuating me is to present our present state of knowledge as far as is warranted by actual, proved facts." He has successfully adhered to this ideal on every page of this valuable monograph. The book falls naturally into two main divisions: First, a succinct summary of the physiology and biochemistry of the ovarian hormones to date. Second, a clear account of the physiology and physiologic pathology of the ovaries and the uterus in women, and the attempts to control and otherwise influence these processes by organotherapy. The book represents the material and conclusions of twenty-five years of laboratory work and clinical experience. The author has persisted in laboratory research and controlled clinical work for this long period despite discouragement that would have paralyzed or silenced most men not driven by the rare and unsatiable curiosity for truth. In this period he has stimulated a number of other workers in the field to undertake such phases of the work that he could not carry out personally, notably the biochemist Dr. R. G. Gustafson.

The author has subjected most of the ovarian preparations now on the market to biologic and clinical assays for activity, and, as was to be expected, in the hands of a competent worker, all of the ovarian preparations to be taken or administered by mouth proved inert. He says, "I have repeatedly put myself on record as entirely sceptical concerning the effect of desiccated, unconcentrated ovarian preparations, and yet the literature teems with glowing reports of the efficacy and the wonderful results obtained with these same biologically inert preparations. These effects vary from the immediate induction of menstruation after long periods of amenorrhea, the complete abolition of annoying and distressing menopause symptoms, to the complete relief of the intractable vomiting of pregnancy, etc. I am unable to account for this irreconcilable discrepancy between biological titer and clinical results, except on the basis of psychical effect, lack of strict criteria and control, and the optimism of both patient and physician."

One of the outstanding puzzles in the present problem is finding in the blood and urine of normal males (man) and in extracts of various plant tissues substances which on injection into spayed rodents or sexually immature rodents produce the same changes in the histology of the vaginal smears as are produced by the ovarian sex hormone. This would seem to indicate that we have to fall back on the ability to produce menstruation and the secondary sex characters in spayed primates as the only reliable biologic assay of the ovarian hormone.

The book is readable and clear. It may be perused with profit by every internist and general practitioner, and the biologic worker in this field will find it a useful source of reference.

DIE GASTROSKOPIE IN RAHMEN DER KLINISCHEN MAGENDIAGNOSTIK. VON DR. KURT GUTZEIT, Privatdozent an der Universitat Breslau. Sonderausgabe des gleichnamigen Beitrages in "Ergebnisse der inneren Medizin und Kinderheilkunde." Volume 35. Price, 9/60 Rm. Pp. 94. Berlin: Julius Springer, 1929.

This brief monograph constitutes a real contribution to the literature of gastroenterology. It is not a manual of gastroscopy, but a discussion of gastric pathology based on the author's own experience. The first twenty-seven pages are devoted to a consideration of the various types of gastroscopes, their advantages and dis-

advantages, the technic, the dangers and the contraindications. It is noteworthy that 500 patients were subjected to gastroscopic study without a single fatality. The remaining seventy pages present the results of a combined gastroscopic, roentgenologic and clinical study. All of the patients were examined roentgenologically as well as gastroscopically by the author himself using the most modern roentgenologic technic. The majority were also observed clinically by him. In this way the results of the different methods were correlated in an effort to obtain as complete a picture as possible of the various disease processes. The discussion centers on gastritis, defects of the mucous membrane and ulcer. The author concludes that the three are indistinguishable symptomatically, that gastritis occurs commonly in the absence of gross mucosal defects, that acute ulcers may or may not be accompanied by gastritis and that gastritis, if present, may be in a different region of the stomach than the acute ulcer. Chronic ulcer, on the other hand, is invariably accompanied by gastritis. The first stage in the healing of an ulcer is a subsidence of the inflammatory reaction. No relationship exists between the severity of the pain and the degree of mucosal alteration either in gastritis or in ulcer.

The diagnosis of gastric carcinoma is discussed and the importance of the various criteria evaluated. Benign gastric tumors are considered. Special attention is given to the problem of gastric pain and to the relationship between mucosal changes and gastric acidity.

The monograph is highly recommended to all those interested in gastric disorders.

THE BIOCHEMISTRY OF THE AMINO-ACIDS. H. H. MITCHELL, and T. S. HAMILTON. American Chemical Society Monograph Series, No. 48. Price, $9.50. New York: The Chemical Catalog Company, Inc.

The authors of this monograph have successfully dealt with the knowledge centering around the amino-acids in a complete and critical manner. They not only have attempted to order the facts about the amino-acids but have assuredly attempted a critical discrimination and reconciliation of conflicting data and theories.

Approximately, the first third of the monograph is devoted to an excellent description of the physical and chemical properties of the amino-acids, their determination in proteins and their individual identification. This section is well illustrated with photographs of the crystalline amino-acids. The tables listing their properties are clear, and the sources of the data are easily identifiable. Methods of determination referred to are described in general terms but not in detail because the authors wisely refrained from making this volume a laboratory guide.

The last two thirds of the book are devoted to the physiology of the amino-acids. The course of the amino-acids from their liberation in the gastro-intestinal tract to their absorption, utilization and final fate is fully discussed. When the work of investigators has been extensive and has had a profound influence on modern points of view, it is discussed in sufficient detail for the reader to gain a clear understanding of the points at issue. Much of the last portion of the book is devoted to problems associated with the metabolism of proteins with particular attention to their nutritive values. At first one gains the impression that this material is irrelevant to the primary purpose of the book, but the reviewer found that, although necessarily curtailed as to detail, this discussion really rounded out what one wanted to know about the place of amino-acids in the field of biology.

The bibliography is extensive, and the book is well indexed.

STERILIZATION FOR HUMAN BETTERMENT. A SUMMARY OF RESULTS OF 6,000 OPERATIONS IN CALIFORNIA, 1909-1929. By E. S. GOSNEY, B.S., LL.B., and PAUL POPENOE, D.Sc. Price, $2. Pp. 201, with index and bibliography. New York: The Macmillan Company, 1929.

This is a timely, accurate and useful digest of the results of the 6,255 eugenic sterilizations in the state of California since the law came into force in 1909. California has the longest continuous record of eugenic sterilization of any state

or country. Dr. Dickinson, Secretary of the Committee on Maternal Health, New York, after an investigation of the operation of the sterilization law of California, stated: "The serious consideration given to the individual patient and the skill in operative work makes the experience in this state very weighty evidence on the whole problem." The authors have succeeded in summarizing the essentials of this experience clearly, objectively and remarkably free from propaganda. In California the operative mortality has been extremely low. A small percentage of the men and women sterilized showed return of fertility. The operation has no untoward effects on the sex life. In California the application of the sterilization law must have been in the hands of the ablest physicians and officials, for we are told that opposition to the law, even among the classes sterilized, is less and less in evidence. "A large part of the public is ready to accept sterilization for itself as well as for others — so much so that a purely permissive and voluntary law would cover most operations."

The first part of the book is devoted to a summary of the facts; the second part to conclusions and general considerations, and the appendixes contain much useful historical and statistical data.

PATHOGENIC MICROORGANISMS. By W. H. PARK, A. W. WILLIAMS and C. KRUMWIEDE. Ninth edition revised. Price, $6.50. Pp. 819. Philadelphia: Lea & Febiger.

The ninth edition of the Park, Williams and Krumwiede "Pathogenic Microorganisms" scarcely needs an introduction to students and workers in bacteriology. For many years the previous editions of this text have been accepted as a standard guide, and the ninth edition ranks with the others. The arrangement of the chapters into three parts is continued in the new edition but with some slight changes. The first part deals with the methods for studying bacteria. Procedures for sterilization, for the preparation of many mediums, for culturing bacteria and for carrying out immune reactions are described in detail and with ample discussions. This part also includes the technic for the complement-fixation tests and the Kahn and the Meinicke tests.

In the second part consideration is given to the individual pathogenic microorganisms, the bacteria in particular, the protozoan parasites and the vegetable forms higher in organization than the bacteria. The chapters on the molds and the yeasts are probably the least satisfactory of the book, and could be improved considerably. Many details of technic and valuable discussions are contained in the chapters of the second part, as well as accounts of diseases produced by filtrable viruses.

Part three deals with applied microbiology, and the chapters therein concern such matters as the bacteriologic examination of water, air, soil, milk, the contamination and purification of water and the standardization of disinfectants.

MEDIZINISCHE PRAXIS. BAND V. RADIUMTHERAPIE, METHODEN UND AUSSICHTEN. VON DR. F. GUDZENT, a. o. Professor an der Universität Berlin. Herausgegeben von Grote, Fromme, Warnekros. Paper. Price, 6.50 marks. Pp. 116, with 53 illustrations. Leipzig: Theodor Steinkopff, 1929.

This booklet serves as a short, concise handbook of reference regarding the indications and usage of radium in medicine. A short résumé of the discovery of radium and of its physical and chemical properties is given. The decay of radium and its emanation is explained, and filtration principles with various types of radium applicators are illustrated and explained.

The biologic response of skin, muscle, tendon, cartilage, bone, nerve tissue and the blood to the action of the rays from radium is reported.

Indications and technic of treatment for gout, rheumatism, neuritis, dyscrasias of the blood and chronic suppuration by inhalations of emanation and by drinking

and bathing in radio-active waters are given; a discussion of the radium content of the waters of various popular German watering places is also included.

The types of lesions of the skin amenable to the action of radium are briefly discussed; for deeper tumors the importance of combined surgical intervention and usage of radium is stressed. The gynecologic uses of radium are fully entered into.

PHYSICAL DIAGNOSIS. By W. D. ROSE, M.D., Associate Professor of Medicine, University of Arkansas, Little Rock, Ark. Fifth edition. Cloth. Price, $10. Pp. 817, with 310 illustrations and three colored plates. St. Louis: C. V. Mosby Company, 1927.

This book, which has been long recognized as one of the standard texts in the subject, now appears in its fifth edition, rather extensively revised and rewritten in many portions, particularly those dealing with the pathologic physiology of the heart and the manifestations of incipient cardiac insufficiency. The illustrations are well chosen and clear, being printed on good paper, and being accompanied by brief explanatory captions, thereby enabling the student to grasp the context readily.

The chapters on examination of the nervous system are too sketchy to be of much value. This, however, is beyond the scope of the usual textbook on physical diagnosis.

This manual is recommended to medical students and practitioners.

DISEASES OF THE STOMACH, A TEXTBOOK FOR PRACTITIONERS AND STUDENTS. By MAX EINHORN, M.D., Emeritus Professor of Medicine at the New York Post-Graduate Medical School and Hospital, Consulting Physician to the Lennox Hill Hospital. Seventh revised edition. Price, $6 net. Pp. 576. New York: William Wood & Company.

This is a new edition of an old book, a thorough text of the old type, abounding in such terms as acute and chronic gastric catarrh, gastrosuccorrhea, myxorrhea gastrica, gastrohydrorrhea, ischochymia, parorexia, choria, sitophobia, gastralgia, gastralgokenosis, hypanakinesis ventriculi, hyperanakinesis ventriculi and peristaltic restlessness of the stomach. Local treatment of the stomach is thoroughly considered, including the gastric douche and spray, the stomach powder blower and the various forms of the electric therapy. The work is essentially clinical. In the opinion of the reviewer, modern gastric physiology and roentgenology should receive much more consideration than is given them.